The New England
Journal of Medicine

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Volume 235 NOVEMBER 14, 1946 Number 20

THE EFFECT OF ANTICOAGULANTS ON THE PENICILLIN THERAPY AND THE PATHOLOGIC LESION OF SUBACUTE BACTERIAL ENDOCARDITIS*

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CHICAGO

THE nature of the valvular lesions in subacute bacterial endocarditis makes the use of anticoagulants appear a logical procedure in the prevention of fibrin formation. Such agents should thereby keep the vegetative process at a minimum and theoretically render the bacteria more accessible to antibacterial agents. Also, in theory, the frequency of embolism should be reduced.

Following the isolation of heparin and the demonstration of its ability to prolong the coagulation time of blood, many workers used this substance alone or in combination with chemotherapeutic and other agents in the treatment of subacute bacterial endocarditis. The results of these efforts are summed up by McLean et al.,[1] Lichtman,[2] Katz and Elek[3] and Hines and Kessler.[4] From his own experience and that of others, Katz concluded that the use of heparin in subacute bacterial endocarditis should be abandoned. Leach and his co-workers[5] were unable to find at autopsy any significant effect of either heparin or the sulfonamides on the valvular lesions; in addition, the vegetations were swarming with organisms.

Because of the reports of McLean and Leach, the use of anticoagulants was not considered in June, 1943, when our studies on the effect of what were then regarded as large doses of penicillin on subacute bacterial endocarditis were begun. But Loewe,[6] who at the same time was studying the effect of similar penicillin dosage (200,000 units a day), was also using heparin, administered intramuscularly in Pitkin menstruum, and considered it essential to success. This opinion was maintained in a subsequent paper.[7] In December, 1943, Dr. Loewe kindly supplied us with sufficient heparin in Pitkin menstruum for a small series of patients. It was our purpose to treat an equal number of patients with and without anticoagulants, such as heparin and dicumarol,|| and also to determine the relative efficacy of the compounds.

Effect on Efficacy of Penicillin

To date, we have employed penicillin in 37 cases of subacute bacterial endocarditis, in all but 2 of which administration was by continuous intravenous drip. The clinical results in the first 34 cases, which furnished the material analyzed in this report, were reported elsewhere.[8] Eight patients received heparin alone, 3 received dicumarol alone, 4 received heparin and dicumarol and 19 were treated without anticoagulants.

When heparin and dicumarol were used in the same patient, one drug was used during half the course of penicillin therapy and the other during the remainder, or one was used during a full course and the other during a subsequent course.

In treating the patient in Case 1, it was found that digitalis partially or completely nullified the effect of heparin. Hence, in subsequent patients, dicumarol was used whenever digitalization became necessary. The pertinent data concerning the patients receiving anticoagulants are summarized in Table 1.

In Cases 1, 3, 4, 5, 6, 7, 8 and 20, all or part of the heparin was administered subcutaneously or intramuscularly in Pitkin menstruum. Whether given subcutaneously or intramuscularly or even in combination with local anesthetics, this material proved so painful that all but 2 of the patients receiving it refused to continue the treatment. Liquid heparin** was therefore added to the penicillin saline intravenous mixture. Determinations of the coagulation time by the Lee–White modification of Howell's method were made daily and frequently twice daily, except in Case 6, in which the capillary method was used. An attempt was made to maintain the coagulation time between 30 and 60 minutes, as recom-

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The penicillin used in this study was furnished by Commercial Solvents Corporation, Terre Haute, Indiana, Schenley Laboratories, Incorporated, Lawrenceburg, Indiana, Lederle Laboratories, Incorporated, New York City and the National Research Council.

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||Supplied through courtesy of Abbott Laboratories, Incorporated, North Chicago.

**The liquid heparin was furnished partly by Abbott Laboratories, Incorporated, North Chicago, and partly by Hoffmann-La Roche, Incorporated, Nutley, New Jersey.

TABLE 1. *Data in Patients with Subacute Bacterial Endocarditis Treated with Anticoagulants in Addition to Penicillin.*

Case No.	Organism	Penicillin Sensitivity of Organism in vitro	Duration of Disease before Penicillin Therapy	Duration of Disease before Combined Penicillin and Anticoagulant Therapy	Daily Dose of Penicillin	Duration of Penicillin Therapy	Daily Dose of Anticoagulant	Duration of Anticoagulant Therapy	Coagulation Time	Prothrombin Time	Vascular Accidents without Anticoagulant	Vascular Accidents with Anticoagulant	End Result	Remarks
		units/cc.	*wk.*	*wk.*	*units*	*days*	*mg.*	*days*	*min.*	*% of normal*				
Patients treated with heparin:														
1	*Str. viridans*	0.02	29	52	150,000–200,000 200,000	60 40	200–300	19	10–75		Multiple emboli sms	Bowel hemorrhage	Death	Autopsy disclosed fibrin-covered tags with enmeshed bacteria.
3	*Str. viridans*	0.06	7	7	200,000 200,000 200,000 450,000	28 20 10 22	150–200	71	20–70		—	—	Recovery	
4	*Str. haemolyticus*	0.04	7	7	200,000	27	100	27	20–60		—	—	Recovery	
5	*Str. viridans*	0.1	8	8	200,000 200,000	27 14	100 200	40	20–65 20–45		Cerebral embolism	—	Recovery	
6	*Str. viridans*	0.02	27	27	200,000	25	50–200	23	4–14		Embolism in viscera and lungs	Embolism in lungs	Death	Autopsy disclosed large, fresh vegetations on the aortic valve and two fresh vegetations on the pulmonary artery, all filled with bacteria.
18	*Str. viridans*	0.04	1½	1½	500,000 2,000,000	33 51	100–300	18	20–65		—	—	Recovery	
19	*Str. viridans*	1.0	4	41	300,000 200,000 250,000 500,000	10 11 90 9	300	9	30–45		—	—	Death	
20	*Staph. aureus*	—	4	30	100,000 500,000	60 8	300 300	8	20		Cerebral embolism	Multiple emboli sms	Death	
Patients treated with heparin and dicumarol:														
7	*Str. viridans*	0.04	30	30	200,000 300,000	29 26	100–200 (heparin) 100–200 (dicumarol) 200 (dicumarol)	60	20–65	100–250	Cerebral embolism	Multiple emboli sms	Death	Autopsy disclosed fibrous remnants of fibrin-covered vegetations on the mitral valve, ulceration of the left auricular wall, with fibrin and bacteria.
8	*Str. viridans*	0.04	16	16	200,000 400,000 400,000	14 15 29	100–200 (heparin) 100–300 (dicumarol) 250 (heparin) 75–300 (dicumarol)	31 26	10–30 40–90		— —	— —	Recovery	This case was complicated by a relapse after eighteen weeks of therapy.
9	*Str. viridans*	0.08	9	9	200,000 300,000	28 27	150–200 (heparin) 100–200 (dicumarol)	29	20–58		—	Cerebral embolism	Death	Autopsy disclosed fibrin-covered, fibrous remnants of mitral-valve vegetations filled with bacteria, as well as a tricuspid ulcer.
21	Atypical *Str. viridans*	0.8*	4	17	200,000 500,000 1,000,000 500,000†	39 41 60 5	150–400 (heparin) 100 (dicumarol)	57	4–17	100–2000	—	Embolism	Death	Autopsy disclosed a stenosed, ulcerated, bacteria-free aortic valve, with multiple myocardial petechial hemorrhages and fibrinous pericarditis.
Patients treated with dicumarol:														
10	*Str. viridans*	0.06	8	8	200,000 400,000	28 28	0–200 0–200	56		135–750 200–450	—	—	Recovery	
16	*Staph. albus*	—	1½	11½	100,000–400,000	64	0–200	11		168–1078	Cerebral embolism	—	Recovery	
13	*Str. salivarius*	0.04	12	32	150,000–2,000,000	273	200–100	3		200	Embolism in kidney	Cerebellar hemorrhage	Death	Autopsy disclosed small fibrin-covered fibrous remnants of vegetations, with bacteria.

*Organism also sensitive to 0.1 unit per cubic centimeter of streptomycin.
†Streptomycin.

mended by Loewe, and it was found somewhat easier to hold it to these limits when liquid heparin was added to the penicillin solution.

By either method of administration there was considerable individual variation in response. In Case 1 the administration of 300 and 200 mg. of heparin subcutaneously on succeeding days resulted in a coagulation time of 20 minutes. The injection of 300 mg. on each of two further days produced a coagulation time of 55 minutes, and no subsequent daily dose could prevent fluctuations from 10 to 75 minutes. Doses of both 200 and 300 mg. a day for periods of three and four days resulted in the same wide variation.

In Case 21 daily doses of 300 mg. for eleven days failed to raise the coagulation time above 18 minutes. In Case 3 alternate daily doses of 200 and 100 mg., given in the penicillin solution, maintained a range of 25 to 35 minutes for eight days, after which the same difficulty was experienced. Later, a daily dose of 150 mg. was found satisfactory.

In Case 4 two consecutive daily doses of 100 mg. in the penicillin solution gave a coagulation time of 50 minutes. After six days heparin was stopped, and for eight days thereafter the range was 20 to 45 minutes. Resumption of 100 mg. a day did not change this finding until a dose of 100 mg. was given subcutaneously, resulting in a coagulation time of 65 minutes.

In Case 5 a daily dose of 100 mg. in the penicillin solution for twenty-eight days resulted in fluctuations between 30 and 55 minutes, with two readings of 65 minutes. Subsequently 200 mg. subcutaneously every other day produced a range of 20 to 38 minutes.

In Case 6 the addition of 100 mg. to the penicillin solution produced a capillary coagulation time of 14 minutes, comparable to a venous time of 46 minutes. A reduction of the dosage to 50 mg. a day produced a range comparable to 13 to 20 minutes for the first three days. Four days later the range increased to 20 to 25 minutes. Thereafter, a subcutaneous injection of 150 mg. daily maintained this range for four days, followed by fluctuations from 20 to 40 minutes. The administration of 200 mg. a day by the same route did not alter this range.

In Case 7, as well as in others, a cumulative effect, impossible to foresee, was observed. The addition of 200 mg. a day to the penicillin solution produced a range of from 10 to 40 minutes. On the fourth day (without heparin) the time was 65 minutes. Two days later a single dose of 200 mg. produced a time of 55 minutes, and thereafter, 100 mg. a day held it between 30 and 40 minutes.

In Case 8 the administration of 100 mg. daily in the penicillin solution held the coagulation time steadily at 30 minutes; 200 and 100 mg., given subcutaneously on alternate days, produced a range of 20 to 30 minutes. During a subsequent course, 175 mg. daily in the penicillin solution produced rapid fluctuations from 20 to 90 minutes for ten days, after which, without alteration of the dose, the coagulation time remained steady between 40 and 50 minutes.

In Case 9 the addition of 200 mg. daily to the penicillin solution was required to produce a range of 20 to 55 minutes, fluctuations between two daily determinations being from 20 to 30 minutes.

When dicumarol was used, an attempt was made to maintain the prothrombin time at 260 to 300 per cent of normal. Daily determinations were made. It was even more difficult to adjust the dose of dicumarol to maintain the desired prothrombin time than to adjust the dose of heparin to maintain the desired coagulation time. As with heparin, considerable variation was found in the individual response to dicumarol. In Case 21 a single dose of 300 mg. of dicumarol developed a prothrombin time 2000 per cent of normal; the same patient had failed to obtain the desired response from heparin, even with daily doses of 200 to 400 mg. for thirty-three days.

A lag of approximately five days from the initial dose of dicumarol to its full effect was observed in nearly every case. Unless this fact is recognized, the prothrombin time for the first few days may lead to overdosage. An initial reduced daily course of 300, 200, 100 and 50 mg. respectively for the first four days, followed by 50 mg. a day, was finally found likeliest to produce and maintain the desired effect.

The duration of the disease before penicillin therapy combined with anticoagulants ranged from one and a half to fifty-two weeks. In 9 cases this was the initial course of therapy. Of the 15 patients receiving anticoagulants, 8 died; it is only fair to say that 2 patients (Cases 19 and 20) were in extremis when admitted. The duration of the disease before penicillin therapy in patients who did not receive anticoagulants ranged from six to forty-two weeks. Of these 19 patients 3 died with active lesions; 1 died of congestive failure, but was shown histologically to have been cured.

The sensitivity of the causative organism to penicillin in vitro ranged from 0.02 to 1.0 units per cubic centimeter in patients receiving anticoagulants, and from 0.02 to 6.0 units in those who did not. Thus the duration of the disease and the sensitivity of the organism to penicillin covered a wide range in both groups.

Effect on Embolism

When the incidence of major embolic phenomena before and during administration of anticoagulants was analyzed, embolism was found to have occurred before but not during administration in 3 cases, both before and during administration in 3, not before but during administration in 2, and neither before nor during administration in 11. Several patients had more than one course of treatment, permitting multiple observations. Thus, whereas anti-

coagulants may have prevented embolism in 3 cases, in 5 they certainly did not.

In 2 additional patients (Cases 1 and 13) massive terminal hemorrhage occurred while anticoagulants were being given. In Case 1 heparin was being used; in Case 13 no anticoagulants were given during eight months of almost continuous penicillin therapy, during which no hemorrhages occurred and only one infarction (in the kidney) was observed. After twenty-four days of 1,000,000 and thirty-eight days of 2,000,000 daily units of penicillin had failed to produce a cure, therapy with 1,000,000 units a day, in addition to dicumarol, was started. On the third day massive fatal cerebellar hemorrhage occurred. At autopsy the left cerebellar hemisphere was found to be destroyed, but the valve showed no friable vegetations (see Fig. 4). The valve lesion in Case 1 was similar (see Fig. 1). Such accidents cannot be dogmatically evaluated in a disease of this nature, but the fact remains that these massive hemorrhages did not occur in any of the patients who did not receive anticoagulants.

FIGURE 1. *Cases* 1 *and* 2.

The photograph on the left shows the fibrin-covered fibrous remnants of vegetations of the mitral valve (A) *in Case* 1, *and that on the right, the same in Case* 2. *The photomicrograph in the middle is of the lesion in Case* 1, *showing bacteria* (A) *enmeshed in fresh fibrin and a polymorphonuclear reaction* (B) *in the adjacent fibrin undergoing organization.*

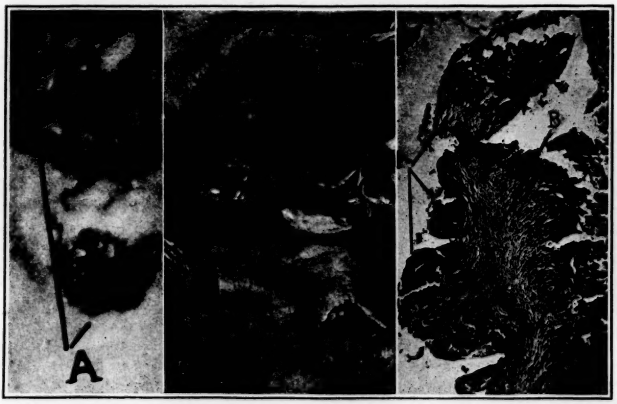

FIGURE 2. *Case* 6.

The photograph on the left shows fresh polypoid vegetations (A) *at the root of the pulmonary artery, and that in the middle, fresh cauliflower-like vegetation* (A) *of the aortic valve. The photomicrograph on the right is of the latter lesion, showing an abundance of fresh fibrin containing myriads of bacteria* (A) *overlying organizing fibrin* (B).

Effect on Recovery

Without regard for any other factors, 4 patients receiving heparin recovered and 4 died. Of the 3 patients receiving dicumarol alone, 2 recovered and 1 died. Of the 4 who received combinations of heparin and dicumarol, 1 recovered and 3 died. Of 19 patients receiving no anticoagulants, 14 recovered; of the 5 who died, 4 were found at autopsy to have healing but still active lesions, and 1 (Case 12) who died of congestive heart failure was clinically and histologically cured.

The most significant factor in recovery is not the use of anticoagulants but the daily penicillin dosage. An analysis of the 34 cases in relation to the daily penicillin dosage, revealed that with daily dosages of less than 400,000 units combined with anticoagulants 6 patients died and 2 recovered — a ratio of 3:1. With dosages of 400,000 units or over in addition to anticoagulants, 1 patient died and 5 recovered — a ratio of 1:5. With dosages of 400,000 units or over without anticoagulants, 4 died and 16 recovered — a ratio of 1:4; these cases included

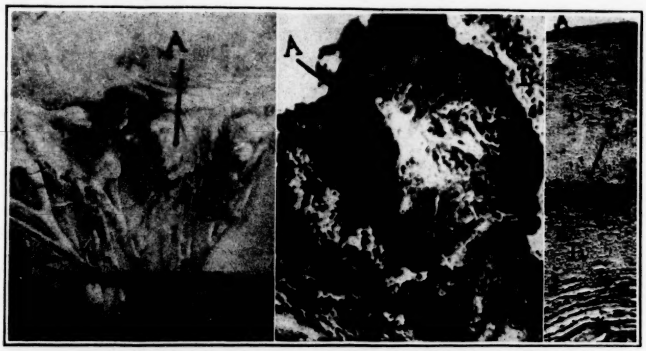

Figure 3. *Case* 9.

The photograph on the left shows the fibrin-covered remnants (A) *of the lesion on the mitral valve. The photomicrograph in the middle shows bacteria* (A) *enmeshed in fresh fibrin and platelet thrombi* (B) *attached to the surface of the fibrin, and that on the right, regenerated endocardium* (A) *overlying organized fibrin* (B), *as well as bacteria* (C) *in the mid-portion of the valve with a more densely organized, and apparently older, layer of fibrin* (D) *beneath.*

Figure 4. *Case* 13.

The photograph on the left shows the fibrin-covered fibrous remnant (A) *of the mitral valve. The photomicrograph on the right shows bacteria* (A) *enmeshed in fibrin overlying calcium.*

that of the patient (Case 13) described above in whom massive cerebellar hemorrhage occurred. If this case, which is difficult to classify, is omitted the ratio of deaths to recoveries in patients receiving 400,000 units or more daily without the use of anticoagulants is again about 1:5. Ten of the 16 patients who recovered ultimately received from 1,000,000 to 2,000,000 units a day. In 5 cases of recovery with anticoagulants and 400,000 units or over and in 3 of similar dosage without anticoagulants, smaller daily doses had not resulted in cure. Hence, regardless of anticoagulants, the turning point in favor of recovery was the increase in the daily dose of penicillin to 400,000 units or more. Excluding Case 13, because of the fatal cerebellar hemorrhage, there were only 2 deaths in 12 patients receiving 1,000,000 units or more of penicillin a day. One of these patients (Case 21) received anticoagulants, and the other did not. The offending organism in the former was an atypical form of *Streptococcus viridans* that was relatively insensitive to penicillin (0.8 unit per cubic centimeter) but sensitive to streptomycin (0.1 unit per cubic centimeter), which could not be obtained until late in the course of the disease. Continuously negative blood cultures could not be obtained, and embolic phenomena continued until streptomycin proved to be the effective antibacterial agent.[9] This experience is in line with that of most investigators regarding the combined use of sulfonamides and anticoagulants — namely, that anticoagulants are of no avail if the antibacterial agent is ineffective.[2-5]

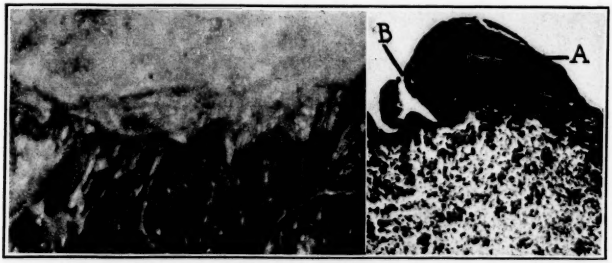

FIGURE 5. *Case* 12.

The photograph on the right shows a grossly healed mitral valve, with no visible fibrin. The photomicrograph on the right shows one of the few scattered areas of fibrin (A) *overlying the almost completely healed valvular lesion; there is a proliferating endocardial cell* (B) *in the process of covering over the minute area of fibrin.*

EFFECT ON PATHOLOGIC LESION

Histologically, no conclusive evidence in favor of the use of anticoagulants could be demonstrated. Grossly, Cases 1 and 2 were comparable. In the former the patient was receiving heparin at the time of death and a coagulation time ranging from 10 to 75 minutes had been maintained for nineteen days previously. During the preceding six months penicillin totaling 15,700,000 units had been given. The patient in Case 2 received no anticoagulants. The involved valve of the heart in both cases showed fibrous tags of vegetations covered by a layer of fresh fibrin (Fig. 1). In Case 1 bacteria were present in the fibrin and deeper structures; in Case 2 no microscopic sections were made.

Case 6, in which the duration of the disease before penicillin-heparin therapy was almost identical with that of Case 1, had the largest, most typically cauliflower-like and friable vegetations of any of the autopsied patients (Fig. 2). Bacteria in large numbers were found in the fibrin, the outer layer of which was fresh. Yet this patient received heparin in daily doses of 50 to 200 mg. during twenty-three of the twenty-five days of penicillin therapy and was heparinized at the time of death.

The disease in Cases 9 and 13 was of about equal duration at the beginning of penicillin therapy (nine and twelve weeks, respectively). The patient in Case 9 received heparin for twelve and dicumarol for seventeen days of the first course of treatment, and dicumarol for nine days of the second course. In Case 13, with a treatment period of eight months, no anticoagulants were administered except during the terminal five days. Grossly and microscopically the lesions were similar (Figs. 3 and 4), but if anything there was less fibrin in Case 13. In Case 9 bacteria were present not only in the fresh fibrin covering the remnants of the vegetations but also in the organized and organizing fibrous tissue of the midportion of the valve; three superimposed layers of fibrin, in varying stages of organization and with bacteria between each layer, were present in one of the valve sections, suggesting that heparin during the first course of penicillin did not prevent fibrin formation.

In Case 12, one of the longest (forty-two weeks) in point of duration of the disease before penicillin therapy, healing of the vegetations took place without the use of anticoagulants. Only a few micro-

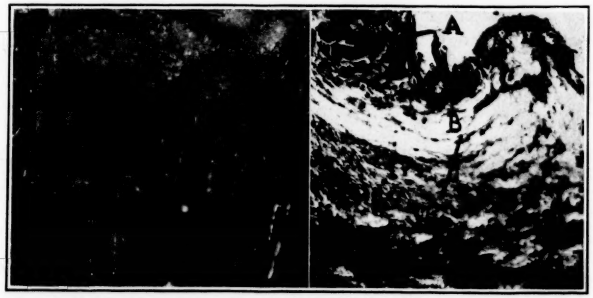

FIGURE 6. *Case* 17.

The photograph on the left shows the fibrin-covered remnants (A) *of the lesion on the mitral valve. The photomicrograph on the right shows cocci* (A) *enmeshed in fibrin, with underlying organizing fibrin and granulation tissue* (B).

scopic layers of organizing fibrin were found, and no bacteria were present (Fig. 5).

In Case 17, in which the disease lasted twenty-five weeks before penicillin therapy was instituted, death occurred from secondary staphylococcal septicemia. mained at the time of the terminal septicemia, it cannot positively be said that the fibrin present at autopsy was not the result of the superimposed staphylococcal invasion. Somewhat comparable was Case 7, in which the duration of the endocarditis before penicillin therapy was thirty weeks and in which heparin was given for seventeen days and dicumarol for seventeen days because digitalization was necessary; during a

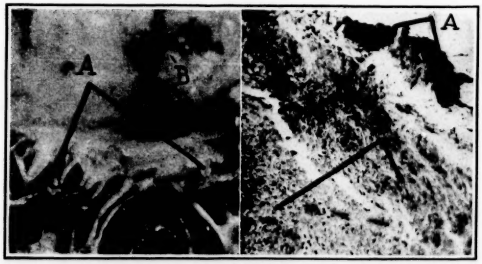

FIGURE 7. *Case* 7.

The photograph on the left shows fibrous pedunculated remnants (A) *of the lesion of the mitral valve, which are covered with small patches of fibrin; there is an ulcerative lesion of the auricular wall* (B), *which also shows scattered areas of fibrin. The photomicrograph on the right shows bacteria* (A) *enmeshed in fresh fibrin on the surface of the valvular lesion and underlying fibrin* (B) *in an advanced stage of organization.*

No anticoagulants had been used during treatment of the endocarditis. The remnants of the vegetation were small (Fig. 6), and although we believed there was clinical evidence that some fibrin re-second course of penicillin, dicumarol was given for twenty days. Grossly and microscopically the lesions (Fig. 7) were similar to those in Case 17.

Summary and Conclusions

Thirty-four consecutive and unselected cases of subacute bacterial endocarditis treated with penicillin constitute the material for this report. Twelve patients received anticoagulants from the outset of penicillin therapy and also during subsequent courses when more than one course of treatment was given. Two, who were admitted in advanced stages of congestive cardiac failure after varying periods of penicillin therapy without anticoagulants, died after combined penicillin and heparin therapy lasting nine and eight days respectively. One, previously treated for eight months without anticoagulants, suffered massive cerebellar hemorrhage three days after a course of penicillin combined with dicumarol had been begun. Nineteen patients were treated without anticoagulants at any time.

Death occurred in 12 cases in the entire series, and autopsy was performed in 10. There were 4 deaths among the patients who received anticoagulants from the outset of therapy, and 4 among those who received anticoagulants twelve, nine, eight and five days, respectively, at the end of long periods of penicillin therapy. There were 4 fatal cases in which no anticoagulants were given. In 1 of these the patient was histologically cured but died of congestive heart failure. The ratio of deaths to recoveries in patients receiving less than 400,000 units of penicillin — all of whom received anticoagulants at some time — was 3:1. The ratio in patients daily receiving 400,000 units or more of penicillin was 2:5 when anticoagulants were used throughout or during part of the therapy, whereas on a similar schedule, the ratio was 1:5 in patients treated without anticoagulants at any time.

In 5 cases anticoagulants failed to prevent major embolism, in 3 prevention was possibly obtained by this means, and in 11 no major embolic phenomena were observed before or during the use of anticoagulants. Of the 19 patients treated without anticoagulants at any time, 6 had major embolism and 13 did not.

We could find no way of determining whether anticoagulants prevented further clotting at the site of embolism.[10]

Gross and microscopic specimens from patients treated with and without anticoagulants are presented. The most typically polypoid and cauliflower vegetations were found in a patient who died at the end of twenty-five days of combined penicillin and heparin therapy. An abundance of fresh fibrin was present on the vegetations. The most nearly complete stage of healing was present in a patient who did not receive anticoagulants. All other lesions showed advanced stages of healing, and yet all showed some fresh fibrin on the surface. The amount of fresh fibrin present on the lesions in patients treated with anticoagulants was not demonstrably less than that on the lesions in untreated patients.

Generally speaking, thrombosis at the site of the intravenous needle was less in the patients receiving heparin incorporated in the penicillin saline mixture. Small amounts of heparin (50 mg.) added to the mixture when the preferable intravenous drip method of administration is used, may aid in retarding venous thrombosis.

Since considerable variation in response to the same dose of heparin or dicumarol was found in the same and in different patients, no standardization of dosage was possible.

No statistical, anatomic or histologic evidence could be found that anticoagulants are a necessary adjunct to penicillin therapy of subacute bacterial endocarditis.

If the daily dose of penicillin is adequate and treatment is continued long enough, healing of the vegetations will take place as well without as with anticoagulants. The rate of recovery was 100 per cent in our latest 15 consecutive cases, in most of which the patients daily received 1,000,000 units or more. All these patients were treated without the use of anticoagulants.

It is doubtful that anticogulants prevent major embolism.

Fatal hemorrhage resulting from the use of anticoagulants was suggested, although not proved, in 2 of the cases.

The additional cost, which is large when heparin is used, as well as the expense and inconvenience to the patient of daily determinations of coagulation or prothrombin time, does not seem justified.

We are indebted to Dr. Eugene Hildebrand for his assistance in evaluating the gross and microscopic lesions.

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FOREIGN BODIES IN THE RESPIRATORY TRACT*

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BOSTON

WHEN the diagnosis of foreign body in the respiratory tract has been established by history, physical examination and x-ray study, the surgeon is presented with a problem whose successful solution consists, of course, in the extraction of the foreign body without harm or damage to the patient. Usually, it is the general practitioner who first sees such a patient, and thus the family physician has the first opportunity to make or to miss the diagnosis. Certain pitfalls must be avoided to prevent diagnostic error and improper attempts at removal. This paper briefly reviews some of the salient features of foreign bodies in the various parts of the respiratory tract.

A foreign body in the nose is rare. It is usually self-inserted, and not infrequently the act is concealed by a child. Unilateral nasal discharge in children means that the presence of a foreign body must be ruled out before other possibilities are considered. Within twelve hours after the lodgment of a foreign body in one side of the nose, the secretion becomes purulent. As the days go on, a fetid odor may develop, and over the months and years a rhinolith may form. Bloody nasal discharge occurs immediately after insertion only when the foreign body is sharp and rough. Foreign bodies in the nose are easily seen if looked for. To remove a nasal foreign body, forceps, which often push the foreign body back into the nasopharynx, should not be used; instead, an L-shaped instrument should be employed. If one can get behind a foreign body and pull it forward, it can be readily removed. Cocainization of the nose makes the procedure painless, and adrenalin provides more space by shrinking the turbinates; general anesthesia is seldom necessary. Unless the patient can be absolutely controlled, however, primary general anesthesia is required. The nasopharynx should be guarded, to avoid pushing the object back to be aspirated. Irrigation of the nose often causes ear infection and fails to dislodge the foreign body.

Foreign bodies in the nasopharynx are also infrequent. The patient must cough or gag to drive the foreign body up behind the uvula into the nasopharynx. The symptoms are pain and discomfort referred to the ears, to the back of the head or neck, sometimes to the laryngeal region and sometimes to the cheeks. In other words, unless the nasopharynx can be visualized with a nasopharyngeal mirror, it is unwise to decide that it does not contain a foreign body. X-ray films demonstrate opaque foreign bodies, such as coins, bones and tacks, but do not show pieces of fruit, nuts or wood. Palpation with the finger is an unsatisfactory method of removal. It should be remembered that if the patient is sitting up, dislodgment of the foreign body may cause it to be lost into the trachea or esophagus or to be pushed forward into the nose. In co-operative adults local anesthesia is quite satisfactory; in children general anesthesia is preferable. The head should be kept low during the operation, and any physician who inspects the results of his adenoidectomies can remove a foreign body from the nasopharynx.

The pharynx and hypopharynx are the most frequent sites for foreign bodies. Ingestion is usually accidental. Because of inability to use the laryngeal mirror, foreign bodies in the hypopharynx are often missed. When the patient complains of pain each time he swallows, a foreign body is present. When there is general soreness that is not made worse by swallowing, the patient has usually suffered only a scratch or abrasion; if the patient gargles a dilute solution of cocaine or pontocaine, the scratch becomes anesthetized and the soreness disappears, but a foreign body such as a bone continues to cause pain on swallowing. This is a simple way to distinguish between an abrasion of the pharynx or hypopharynx and the actual presence of a foreign body. Unless the hypopharynx is carefully inspected with the laryngeal mirror, a foreign body may not be found. The roentgenologist has difficulty in seeing small fishbones imbedded in the base of the tongue or at the bottom of the tonsillar fossa; these are clearly visible with the laryngeal mirror. Once a foreign body has been seen in the pharynx or hypopharynx, hasty grasping must be avoided, since a fumble means its loss. Often, three hands are required for a successful extraction, — one hand for the patient's tongue, one for the laryngeal mirror and one for the forceps used to grasp the bone, — and sometimes an additional pair of hands is needed to hold the patient's head. An example is afforded by a case in which an attempt to grasp, by means of a tongue depressor and a hemostat, a pin visible in the pharynx caused the pin to land in the tracheobronchial tree, where, of course, the problem was much more difficult than the one presented by the pin at its original site. In another case, which emphasizes the fact that more harm than good can be done by working under adverse circumstances, a sixteen-month-old baby was seen by its mother to cough and choke after having placed something in its mouth. A physician who examined the child be-

*Presented at the annual meeting of the Massachusetts Medical Society Boston, May 21, 1946.

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lieved that there was a wheel from a plastic toy lodged in the hypopharynx and therefore suggested sending the child to the hospital for removal. The mother demurred and called a second physician, who said that with a tongue depressor he could see a disklike object in the hypopharynx that could be grasped with the fingers but could not be dislodged. After unsuccessful efforts for an hour with a can of ether, a flashlight, a tongue depressor and the fingers, the child was taken to the Massachusetts Eye and Ear Infirmary, where a laryngoscope and forceps were requested, to remove the disk, which had some sort of protrusion on its inferior surface. X-ray films were taken in spite of the fact that the physician considered them unnecessary. The films demonstrated the eye of a toy bear imbedded, with the large end in the hypopharynx and the pointed portion, used to hold the eye in the bear, penetrating the pharyngeal wall and extending down into the soft tissues of the neck. In the pharynx above the eye, a laceration about 2.5 cm. long and 0.6 cm. wide was observed. Manipulation had resulted in a tremendous amount of air emphysema in the soft tissues of the neck; this extended into the mediastinum around the heart and up to the base of the skull. After extraction of the foreign body and the administration of penicillin and sulfadiazine the patient made an uneventful recovery. This case emphasizes the value of x-ray examination and the fact that extreme caution must be observed in manipulating a foreign body.

A foreign body in the larynx is rare. If a foreign body of any appreciable size lodges in the larynx, the airway is obstructed and the patient dies promptly, before help can be given. The object, however, may be small enough so that the patient can breathe around it, but whenever a foreign body prevents the vocal cords from approximating normally, hoarseness results. It is too often forgotten that hoarseness means trouble with the organ of speech, the larynx. A case in point is that of a twelve-month-old child with a history of increasing cough and hoarseness of four weeks' duration in which x-ray examination demonstrated a safety pin between the vocal cords. It was apparent from these films that the pin was pointed up and that the point was imbedded anteriorly in the base of the epiglottis. When I saw this x-ray film, I doubted the mother's statement of four weeks of hoarseness. The larynx was exposed without anesthesia, and it was seen that the blackened, corroded head of a safety pin in the posterior portion of the glottis was almost completely surrounded by red granulation tissue. I attempted to remove this pin by grasping the head and holding the point with the tip of the laryngoscope. After carrying out this procedure, I discovered that I had the head and the back of the safety pin, but that the spring and the pointed end were missing. Inspection of the larynx did not reveal the remainder of the pin. The child was taken to the x-ray room, where films demonstrated the remainder of the pin in the right main bronchus. A bronchoscope was inserted, and the portion readily removed. The corrosion and brittleness of the pin offered sufficient proof that the mother's statement regarding the four weeks' duration was reliable. Without the x-ray examination and many pieces of equipment, this case might have been difficult. Thus, it is essential that the removal of any foreign body from the larynx or below be done in a hospital equipped to deal not only with the particular situation but also with all possible complications.

Foreign bodies in the trachea challenge diagnostic ability, unless they are radiopaque, when they are easily diagnosed by x-ray examination. But the diagnosis of a nonradiopaque foreign body in the trachea is made by the history and physical signs. Even in the youngest children, the pathognomonic signs are a sudden stopping of the expiratory air blast, with cessation of phonation and paroxysmal cough, followed by relief with a good airway and good phonation. Large seeds or shells of nuts produce these signs. Recently, a three-year-old child coughed and choked when he fell while eating. He was taken to another hospital, where a variety of studies, including x-ray films, were carried out. He was discharged and then returned to the hospital for a stay of another week. Periodically he had attacks of cyanosis associated with coughing and wheezing, and because of one of these he was rushed to the Massachusetts Eye and Ear Infirmary for an emergency tracheotomy. On arrival, the signs had subsided. Shortly after admission, they recurred and then disappeared. A large piece of pistachio-nut shell was removed from the trachea through a 5-mm. bronchoscope, and the child was subsequently symptom free.

Foreign bodies that are aspirated usually do not move up and down in the trachea but become lodged in one of the main bronchi or, if small, go farther into one of the smaller bronchi. It is not so much the actual diagnosis of foreign body in the bronchus that is difficult as it is the consideration of the possibility. The physician not only forgets to ask about the possibility of a foreign body but also, too often, fails to believe the patient's own story. An x-ray film, which is easy to take and inexpensive, often explains an atypical case of pulmonary disease. The physical signs of bronchial obstruction are well known. In time, bronchial obstruction leads to suppuration, with fever, chills, cough and sputum. Although an x-ray film of the chest leaves no doubt that a radiopaque foreign body is present, it is equally effective in revealing nonradiopaque objects that have been in place for a long time. If a foreign body causes only narrowing of the bronchial lumen, a wheeze is the cardinal sign. Irritation of the bronchial tissues by a foreign body results in swelling and a further narrowing of the lumen so that air passes the foreign body on inspiration, with dilation of the bronchus; on expira-

tion, however, the outlet closes as the bronchus constricts, and air trapping distal to the foreign body develops. This is emphysema. When the foreign body has been in place long enough to block the bronchus completely, the emphysematous air distal to the foreign body is slowly absorbed, and collapse of that segment of the lung occurs. Expiration and inspiration films are a substitute for fluoroscopy. Fluoroscopic examination of a patient suspected of a foreign body in the bronchus is always indicated, because it is often difficult for the x-ray technician to obtain full expiration and inspiration films. On expiration, air leaves the one but not the other lung, which remains full and demonstrates air trapping in the main bronchus. Such expiration and inspiration films are diagnostic of a nonradiopaque foreign body in the main bronchus. Without bronchial obstruction a foreign body can be in place for a long time without infection. A pin, for example, may remain for years in the lung without causing trouble unless it perforates a vessel or creates granulations that block a bronchus. It is bronchial obstruction that causes harm and permits infection to become rampant.

* * *

The diagnosis of a foreign body in the respiratory tract is easy when one remembers to think of the possibility. The story of the patient or that of the patient's family should be believed until proved wrong. X-ray examination should include the entire respiratory and digestive tracts. Fluoroscopy of the chest is indicated when a nonradiopaque foreign body is suspected. Unless a foreign body can be completely visualized, it is dangerous to attempt its extraction. The safe removal of a foreign body is aided by the possession of a duplicate, as well as x-ray study, so that its exact position and location are understood. Only then can removal be accomplished without the possibility of doing more harm than good through unwise manipulation. Extractions of foreign bodies are best done where there is an adequate armamentarium to deal with any complication that may arise.

BOSTON MEDICAL LIBRARY

Report of the President*

THIS annual meeting marks the end of my five-year tenure of the office of president, the first two having comprised the unexpired term of my predecessor and the last three the regular term prescribed by the by-laws. Since I could not accept renomination if it were offered, it is appropriate that I should render a brief account of my stewardship, with special reference to the state of the Library and to plans that are under consideration for its future.

First, I ask you to pay silent tribute to the following eight fellows who died during the year: Hugh Cabot, Charles H. Lawrence, Jr., Charles T. Porter, Abraham Rudy, Philemon E. Truesdale, Hugh Williams, Robert S. Hurlbut and Robert Sanderson. Worthy of note as examples of long-continued, loyal support are the forty-seven-year and forty-two-year memberships, respectively, of Dr. Cabot and of Dr. Truesdale. In this connection I am reminded of a physician who would not wish his identity to be known who, at the age of eighty-three and a fellow for many years and long retired from practice, submitted his resignation; on learning of our financial needs, however, he withdrew the resignation and doubled the amount of his annual dues.

Secondly, I have the privilege of making grateful acknowledgment, personally and on behalf of the Library, to the trustees and executive officers who have served with me, to the resident staff and to individuals and organizations who have continued their loyal support. The Trustees, although they are busy with public and personal obligations, have served on committees and pooled their wisdom for our benefit; our secretary, our treasurer and above all our librarian have discharged their duties with no compensation except that of an approving conscience, and our resident staff, depleted in numbers, overworked and perhaps underpaid, under the directorship of Mr. James F. Ballard (now in the fifty-fourth year of his service) have serviced our collections and, so far as humanly possible, adequately met the needs of readers, students and researchers. The Massachusetts Medical Society, whose organ, the *New England Journal of Medicine*, is edited on our premises, and whose executive officers and committees share our building, brings us prestige and support in return for our services and help; likewise the *Journal of Bone and Joint Surgery* and many special societies make use of our facilities to our mutual advantage.

The last five years comprise the entire period of the participation of our country in World War II, together with the months of disruption of normal peaceful activities immediately preceding and succeeding it. Perhaps a total world war is sufficient excuse for any enterprise such as ours not only to fail to advance but also to develop structural and functional weaknesses. Friends of the Library who have read the reports of the president and of the librarian for the last four years are familiar with the matters that have preoccupied us, among which are the conversion of our heating system from oil

*Presented in part at the annual meeting of the Boston Medical Library, March 5, 1946.

to steam, structural alterations to meet the needs of the Massachusetts Medical Society and the *Journal of Bone and Joint Surgery*, the establishment of the James F. Ballard Publication Fund, the issue of a catalogue of our incunabula and manuscripts and the promotion of an elaborate survey of the various medical libraries in Boston. But also since the beginning of the administration of my predecessor, or for at least twelve years, your officers have been anxiously occupied with the problem of conducting a dynamic and expanding enterprise under the handicap of originally inadequate and steadily diminishing financial resources. The Library, ranking second or third in the United States in the value of its collections and the potential importance of its services, is conducted with heart-breaking economy on a yearly income of about $30,000. It should have resources of at least double that amount, together with a corresponding capital sum for completing and improving our still unfinished house. We are seriously in arrears in the purchase of current texts, in subscriptions to periodicals, in binding and rebinding and in cataloguing, and there is literally no room for accessions except temporary installations in the basement and corridors. Only the invincible optimism of our librarian, Dr. Viets, and the efficient industry of Mr. Ballard and his staff have kept up our courage and maintained the library service so well that there have been scarcely any complaints. The details of our physical condition have been so well presented in previous reports that they may be omitted here.

It is the almost unanimous opinion of your officers and their advisers that the provision of facilities for the collection, housing, circulation and preservation of the literature of the medical and allied sciences in any geographic area should be conceived on broad principles of co-operation and mutual assistance among the various interests involved, instead of the individualistic development of a number of essentially similar units all situated within a mile or two of each other. At the turn of the century, when ours was the only considerable collection in this vicinity, it seemed reasonable that the library should continue its independent career, supported by bequests and gifts and by its fellows and members. Later, a plan to build about it as a nucleus an elaborate academy of medicine, enthusiastically advocated by a group who went so far as to secure an option on land and to obtain an architect's services, was reluctantly given up because of the expense involved, which ran into millions of dollars. During this time there came into being the working libraries of Boston University, Harvard and Tufts College medical schools, as well as the libraries of several major hospitals and numberless small collections of individual investigators and teachers; one of these is well known actually to rival our library in size and usefulness. The survey and resulting plan, designated by us as the "Fleming-Metcalf Plan," which aimed to integrate and develop these elements into a co-operative and mutually beneficial system, has been approved by the authorities of the three medical schools and its consummation actively pressed by your officers. Briefly, the plan envisaged the gift of a large sum by a charitable foundation for capital expenditure, the raising by the Library of a similar sum by subscription among the medical profession and other friends for endowment and the contribution annually of substantial contributions by the working libraries of medical schools and hospitals in return for our service as a central reference and research library ready to supply the needs of the smaller units beyond those of the everyday requirements of faculty, students and staff, and to make unnecessary the expensive enlargement of their physical plants. This plan had the invaluable support of Mr. Metcalf, Director of Libraries of Harvard University, and the tentative approval of the administrators of the three medical schools. Unfortunately, the members of the foundation, although approached by one who had their ear, found themselves unable to embrace the opportunity. Several other sources were unresponsive. Your officers and committees reluctantly concluded that without this aid the project as planned could not be realized.

Another plan is now under consideration — one that for some years has been tentatively suggested and as often put aside as possibly presenting peculiar difficulties. It is nothing less than a proposal of honorable marriage to a contemporary of the Library, quite similar in age, outlook and ambition for future accomplishment. Perhaps, since the prosecution of this suit must rest in the capable hands of my successor, I should not mention it, but after all I have sat in at preliminary talks among the old folks and it is well that the community should get used to the idea.

The Boston Medical Library and the Massachusetts Medical Society have much in common. Perennially young though they may be in spirit, they are perhaps the oldest of their kind in the country, if we date the former from the Second Social or Boston Medical Library, organized in 1803 by the Medical Improvement Society, under a statute of 1798. The statements of their aims as inscribed on their charters are practically identical. The fellows of the Library are almost without exception members of the Society. In 1876, when the Library moved from its two rooms in a basement in Hamilton Place, furnished with two tables, thirteen chairs and some bookshelves, to a little remodeled house at 19 Boylston Place, among the distinguished speakers at the dedication ceremonies was Dr. George H. Lyman, president of the Society. Soon the books accumulated by the Society — 1500 in number — were turned over to the Library. Almost from the first the Council of the Society met in the meeting hall, followed by the Suffolk District Medical

Society and by various committees and other groups. At present the Society's executive offices and the editorial rooms of the *New England Journal of Medicine* are in our building, an arrangement that contributes much to the efficiency and prestige of both.

The exact nature of the proposed alliance will require careful study. Many of the older fellows would be sorry if the Library lost anything of its distinguished identity, a misfortune that could not occur to the Society. The Library has assets valued at between one and two million dollars, depending on the appraisal of irreplaceable files and memorabilia. It is a corporation, and the title of its property is vested in the fellows, who constitute the corporation and whose dues are an important source of income. Nearly all the fellows of the Library are members of the Society but about four fifths of the latter are not fellows of the Library, although they would be perfectly eligible if they so desired after the formality of proposal for membership and action by the Committee on Elections had been complied with. If the Society wished to make a substantial annual contribution to the support of the Library, the comparative status of members of one and fellows of the other would require definition and adjustment. As a matter of fact, the Library has always extended a warm welcome to all reputable physicians — indeed to all citizens — to use freely its facilities and enjoy its privileges, except only those necessarily pertaining to actual ownership or to its status as trustee under wills and bequests.

This is not the place to elaborate on the legal and practical problems raised by this plan. If its realization seems wise, these problems can be solved by men of good will. The broad and liberal view seems to be that we have two organizations whose purposes are essentially identical in striving to promote the public health, each with an enviable record of unselfish service over many years. One has a plant and collections of stored medical knowledge second to but few in this country but lacks endowment and other income adequate for its support; the other, through its numerical strength and wide influence, is able to contribute that support. As one who for nearly forty-five years has been active in the affairs of both these organizations and who has the deep conviction that the prestige and strength of each would be promoted by a close alliance, I have no hesitation in urging that its feasibility be explored to the end that its consummation be accomplished at the earliest possible moment, for time is of the essence now that, after the disruption of War, the institutes of peace are to be restored.

DAVID CHEEVER

Report of the Librarian*

WITH the end of the war and the return of men from the services, the Boston Medical Library is slowly regaining the position it held five years ago. By the beginning of 1946 the membership had already increased and had reached a total higher than that at any time in the history of the Library. During the year, the staff remained unchanged and the Library continued to function at a decreased pace but serving its clientele in what appears to have been a reasonably satisfactory manner. At least no major complaints were heard by the librarian and although many of our services were, of necessity, restricted and we were cut off almost entirely from foreign medical literature, books as well as periodicals, we extended our holdings in English-language periodicals and made an attempt to keep abreast of the times. Much of our foreign-language material, which is being stored abroad, will presumably be made available to our readers in 1946. The German material is entirely lost, but it is quite possible that the paper on which it was printed was so inferior that binding would not have been advisable; these missing periodicals may now be reprinted or duplicated in some form on better paper so that they will have a chance of survival.

*Presented in part at the annual meeting of the Boston Medical Library, March 5, 1946.

The librarian thought the time fitting to give a brief review of the various departments of the Library, covering a period of ten or more years. A discussion and tables on periodicals, binding, membership, use of the Library and size of the Library are therefore included in this report, in addition to the usual departments of book reviews, publications and a statistical evaluation of the contents of the Library as of December 31, 1945.

THE LIBRARY FROM 1936 TO 1945

Periodicals

The current medical literature is largely in periodical form, and the greatest use of a library such as ours is found in this department. The total number of periodicals received in 1945 was 578, only 44 being in languages other than English. Our average from 1930 to 1940, before the war, was about 800 to 900; in 1930, for example, we received 870, and 410 (nearly 50 per cent) were in foreign languages. Since about 1937, by arrangement with the Harvard Medical School Library, we have specialized in clinical journals. It, in turn, has expanded into the fields of public health, dentistry, biology, basic sciences and ophthalmology (Howe Library). This collaborative effort reduced our total number of

periodicals by about 100. During the war, with most of the foreign journals omitted, the number fell as low as 466 in 1944. In 1945 the number of periodicals increased to 578, without most of the more than 400 foreign journals previously received. We have some reason to suppose that our back files of foreign-language journals, except for the German periodicals, are intact in Europe and awaiting shipment to Boston. Our stock of German journals was probably lost by bombing. According to our latest information, the French, Italian, Dutch and Scandinavian periodicals are awaiting clearance and shipping space. Russian journals are now arriving in good number by way of exchange. When we know the cost of our foreign-language stock now abroad, we shall again ask aid from the special societies, which have made generous donations in the past for this purpose.

About 150 journals come to us each year from the *New England Journal of Medicine*, received by them in exchange. When the paper shortage is less and a greater number of issues of the *Journal* can be printed, this list may be expected to increase. The Library could use 50 or more subscriptions of the *Journal* to advantage, and the editor, as always, extends a generous hand in our direction.

Binding of Periodicals

Until about 1937 the Library bound nearly all the periodicals received each year — a total of approximately 900 volumes. Since that date we have had to curtail this activity for financial reasons and now only bind in permanent form 50 to 60 per cent, the others going into temporary binders. Thus, in 1945, only 360 of the 578 periodicals received could be bound. This is naturally disturbing to the librarian, and although it does not preclude the use of these journals, a backlog of journals requiring binding is being built up that we can hardly afford, if the Library is to remain in a workable condition. Since the periodical files are used more than any other division of the Library, permanent binding is almost essential.

Size of the Library

The number of books in the Library slowly approaches 200,000, a total of 199,135 being reached in 1945. The collection of pamphlets, numbering 135,195, grows only gradually, since reprints of papers occurring in the current literature are no longer catalogued. Nearly 3000 books, including 700 bound volumes of periodicals, and over 1000 pamphlets were added in 1945. To catalogue these items, more than 10,000 cards were used.

Plans must shortly be made to provide additional space for our growing collections. This could be done in a number of ways. We have room in our own building for seven more tiers of stacks, which should be built, if funds could be found, for this would be a natural way to house our collection. Secondly, we might transfer the 10 to 20 per cent of our collection that is seldom used to the Harvard University Deposit Library. The cost of storage is relatively low, and items so stored can be removed for use in the Library in a few hours. Thirdly, if a new library is provided in the near future for the Army Medical Library in Washington and it is allowed to become a national medical library, with appropriate borrowing privileges extended to us, we might take from our shelves certain rarely used material, particularly in the nonclinical sections, and deposit it in Washington.

All these plans have good features, and some use of each is probably the best method of handling the problem. By 1950 the librarian hopes to see the stacks completed, some of our collection transferred to the Harvard University Deposit Library, our basement cleared of duplicates and our arrears dissolved. If someone will give us the tools, in the form of funds, the staff, augmented by new personnel, will do the job.

Use of the Library

Both the circulation — that is, the number of items taken from the shelves for use by readers — and the attendance increased in 1945 over 1944, the former from 29,949 to 31,298 and the latter from 7021 to 7100. The circulation in 1945 was approximately that of the average for the last ten years, but we have had during this period, for some reason not fully explainable, a wide swing from about 25,000 to 47,000. The attendance in 1945 was only about 70 per cent of its normal level of 10,000 a year, but it is expected that, with members rapidly being demobilized, the number will rapidly increase. If 10,000 readers use 35,000 items in a year, the Library, as now constituted, is giving a reasonable service. The space for reading in Holmes Hall and elsewhere is rarely used to its limit, since most members call for books and periodicals to use at home or in the office. About 7 out of 10 readers using Holmes Hall are nonmembers.

Membership

The total membership in the Library rose to a new height in 1945, the figure being 932. Fellows constitute about 70 per cent of this total. We have been slowly increasing our membership since 1930, particularly in the years since 1937. There is nothing artificial about our growth, and the increase in numbers indicates a healthy condition, in spite of our numerous and indeed obvious weaknesses. It is hardly a sign of decadence when an increasing number of doctors find it profitable to use the Library and to pay for doing so. The growth speaks well, moreover, for the continued success of the active Membership Committee, but I doubt if even they could hold the membership to its present level if the Library did not offer a reasonably good service. The large increase in the professional members,

from 17 in 1944 to 31 in 1945, is directly attributable to the energetic work of the Membership Committee.

Special Accessions

As usual our restricted funds for special types of books were expended for the purposes designated by the various donors. That a considerable portion of our book funds are so entailed leads to a belief that the Library is primarily an antiquarian institution, with little interest in current medical literature. This is not the case, although we are particularly fortunate in having more funds than most libraries to be diverted into channels other than the more frequent one of acquiring the latest texts and monographs. This we also do, so far as our income permits. More funds are urgently needed for current literature, and until we have them some fields of medical advance will not be fully covered by our accessions. We are relatively strong in our chosen field, clinical medicine, and by co-operation with other libraries all fields are fairly well covered in the Boston area. In the special groups, however, we have continued to buy a considerable number of important books, and in some cases to catalogue previous purchases.

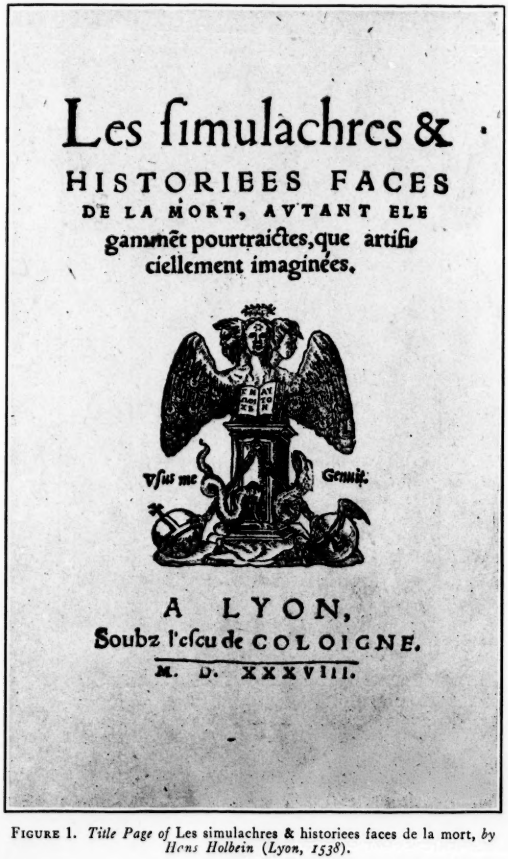

FIGURE 1. *Title Page of* Les simulachres & historiees faces de la mort, *by Hans Holbein (Lyon, 1538).*

Sixteenth-Century Imprints

Among the foreign imprints of the sixteenth century, we have acquired *Les simulachres & historiees faces de la mort* by Hans Holbein (Fig. 1). This book, the first edition of Holbein's *Dance of Death*, was published in Lyons in 1538. It is illustrated with forty-one small woodcuts, as fine as copper plates, probably made from Holbein's drawings by Hans Lützelburger. Warthin,[1] who describes the book in detail, although with a number of errors, states that more than a hundred editions, as well as copies and imitations, are known, following this first printing in book form in 1538. The *Totentanz* or *danse macabre* was a favorite subject for the Renaissance illustrators, and Holbein's figures, or imitations of them, occur frequently as initial letters in books of the sixteenth century.

Often reproduced in medical literature is the drawing of the skeleton, Death, calling on the physician in his study (Fig. 2). Beside the doctor lies his dog. Death leads in an elderly, sick man for consultation with the physician, bringing the urine bottle for casting. The sharp-nosed doctor is not perhaps our ideal physician, but he is obviously a student and the old man, the patient, is a figure of great charm. Warthin describes Holbein's technic as follows:

> In the Holbein cycle the art of the *Totentanz* motive reached the highest point of its development. Nothing has since approached it, either in inspirational value, human interest, or in skill of technic.

The sweating sickness, a fatal epidemic disease running a rapid course, first appeared in England in 1485.[2] A second, less severe epidemic was noted

FIGURE 2. *Holbein's Drawing of the Physician, Death and an Elderly Patient in the First Edition of* Les simulachres & historiees faces de la mort (*Lyon, 1538*).

in 1507, and a third, in 1517, was particularly grave in Oxford and Cambridge. In 1528 another epidemic occurred in London, driving the court of Henry VIII from his residence. From England it spread to Europe, first to Hamburg and then into France and Italy. The so-called "English sweat" never appeared in Europe thereafter, but an epidemic in England, in 1551, was described by John Caius in his famous book published in 1552.

The Library added an account of this disease published within two years of the Hamburg outbreak, which began on July 25, 1529. Joachim Schiller, born at Herdern, near Freiburg, was in practice when he published, in 1531, *De Peste Brittannica* (Fig. 3). The European epidemic ended in November, 1529, apparently as rapidly as it had begun. Schiller's work, a pamphlet of twenty-five leaves, is a scholarly discussion of the disease, without much historical importance. He gives no real description of the epidemic of 1529.

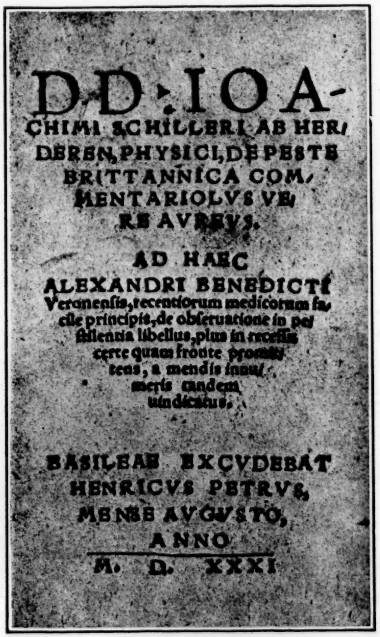

FIGURE 3. *Title Page of* De Peste Brittannica, *by Joachim Schiller (Basle, 1531).*

Otto Raut, an astrologer, who issued a prognostication for the years 1502 and 1503, also wrote, in 1501, a treatise on syphilis entitled *Malum Francie*, which has been acquired by the Library. He was, of course, writing from Ulm, in Germany, and used the common appellation of the time. His book, published in Hagenau, appears to be rare, since only one other copy is recorded, in the library at Zwickau (at least it was so noted before World War II). It is interesting that the manuscript from the Ulm physician crossed the Rhine to be printed in Hagenau by Heinrich Gran, a well known printer of fifteen-century medical books. The syphilis tract is a brief account of five pages.

Hugo Senensis (Ugo da Siena) was one of the most prolific of the medical writers of Italy. He taught at Siena, Bologna, Parma and Pavia and gave lectures at the Sorbonne. One of the earliest physicians to write in the common tongue, his *Trattato* is a justly celebrated incunabula, first printed at Milan in 1481. The original edition is in the Library (No. 383 in the Ballard catalogue[3]). A later printing (Milan, 1508) in Latin was added to the Library in 1945, with an interesting woodcut on the title-page depicting doctors and astrologers in consultation (Fig. 4).

English Imprints

Seven books, printed in London before 1640, were added. One was a partially recorded early printing, probably the first edition, of a work by J. Fletcher entitled *The Differences, Causes, and Judgments of Urine* (Cambridge, 1598). There is an imperfect copy in the library at Cambridge, England.

Spanish Imprints

Nine books were added to this class, including a treatise on physiology written by the Mexican, M. J. Salgado, in 1727.

Americana

Of particular interest are the *Armory Square Hospital Gazette*, published by a Washington hospital in 1864–1865, the *Medical Inquirer*, a botanic journal issued in Fall River and Middleboro in 1846–1847, Joseph Warren's 1772 and 1775 "Oration" and an engraved card, "Entitles to Kine Pock Inoculation," signed by Benjamin Waterhouse.

Modern Manuscripts

The *Letter Books* of Julius Griffiths, in four volumes (1810–1829), and the *Records of the Rutland County Medical Society, 1816–1829* (Rutland, Vermont) were added.

Incunabula

Three incunabula were added, two of which are not recorded in the Stillwell *Second Census*: the *Commentaria in Platonem*, by Marsilius Ficinus (Florence, 1496), and the *Quaestiones Naturales* (Cologne, *circa* 1500).

Library Activities

Book Reviews

Owing in part to the fact that many of our regular reviewers were still in the service, only forty of the two hundred and twenty-six books received from the *Journal* in 1945 were given extended review notices. The other hundred and eighty-six were allotted short reviews or summaries. Eighty-three reviewers, whose names are listed in the two annual index numbers of the *Journal*, gave a valuable service to the Library. Mr. Ballard, as in the past, carried the brunt of the work on the short notices.

Exhibits

During 1946, the following exhibits were set up in the entrance lobby of the Library:

Roentgen, Konrad. In commemoration of the fiftieth anniversary of the discourse of the x-ray (November 8, 1895).

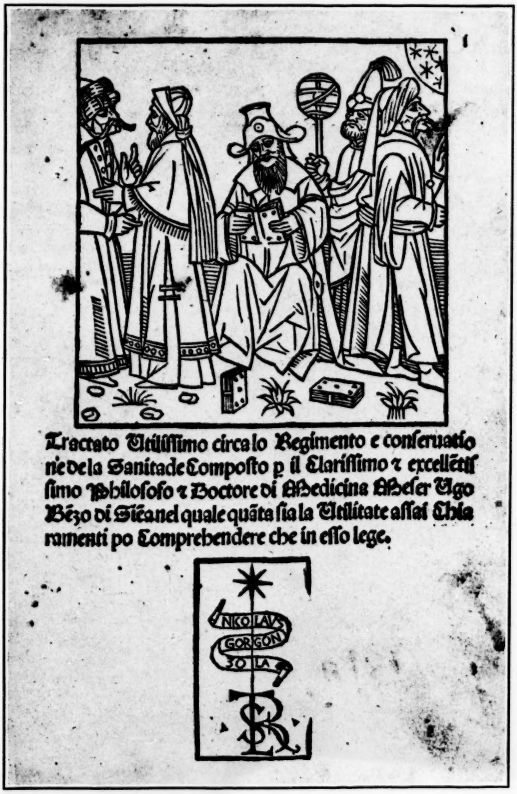
Tractato Utilissimo circa lo Regimento e conservatio
ne de la Sanitade Composto p il Clarissimo z excellētis
simo Philosofo z Doctore di Medicina Maestr Ugo
Bēzo di Sīcanel quale quāta sia la Utilitate assai Chia
ramenti po Comprehendere che in esso lege.
NIKOLAVS
GORGON
SOLA

FIGURE 4. *Title Page of* Tractato Utilissimo circalo Regimento e conservatione de la Sanitade, *by Hugo Senensis* (*Milan, 1508*).

Dürer, Albrecht. An exhibition of five editions of his book, *Human Proportion*, including the first edition (Nuremberg, 1528).

Cornwall, Dean. Series of paintings of outstanding American medical events.

Publications

Recent articles emanating from the Library are as follows:

Editorial. Medical classification scheme of Boston Medical Library. *New Eng. J. Med.* **232**:332, 1945.
Editorial. Doctor illustrates his travel notes. *New Eng. J. Med.* **232**:437, 1945.
Editorial. Medical bibliography. *New Eng. J. Med.* **232**: 686, 1945.
Sixty-ninth Annual Report of the Boston Medical Library for the Year 1944. 36 pp. Boston: privately printed, 1945.
Editorial. Boston Medical Library. *New Eng. J. Med.* **233**: 542, 1945.
Cheever, D. Report of the president, Boston Medical Library. *New Eng. J. Med.* **233**:520, 1945.
Viets, H. R. Report of the librarian, Boston Medical Library. *New Eng. J. Med.* **233**:521-527, 1945.
Editorial. Albrecht Dürer and anatomy. *New Eng. J. Med.* **233**:605, 1945.
Editorial. Marion Sims and his silver sutures. *New Eng. J. Med.* **233**:631-633, 1945.
Viets, H. R. *A Museum in a Medical Library.* 7 pp. Boston: privately printed, 1945.

Miscellaneous

There were no staff changes in 1945, our six regular employees continuing to give the best service possible under restricted conditions. Ten, or possibly twelve, people are needed to run the Library in a satisfactory manner.

The Massachusetts Medical Society, the Boston Society of Psychiatry and Neurology, the Suffolk District Medical Society, the New England Heart Association, the Boston Surgical Society and the Boston Medical History Club met, as usual, in the Library.

Our cordial relations with our close associates in the building, the Massachusetts Medical Society, the *New England Journal of Medicine* and the *Journal of Bone and Joint Surgery*, were maintained.

The director and the librarian attended meetings of the honorary consultants of the Army Medical Library, Washington, D. C., and the librarian delivered an address at the dedication of the Dittrick Museum in the Cleveland Medical Library on October 6, 1945.

HENRY R. VIETS

REFERENCES

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2. Hecker, J. F. C. *The Epidemics of the Middle Ages.* 380 pp. London: Sydenham Society, 1846.
3. Ballard, J. F. *A Catalogue of the] Medieval and Renaissance Manuscripts and Incunabula in the Boston Medical Library.* 246 pp. Boston: privately printed, 1944.

MEDICAL PROGRESS

DISEASES OF THE THYROID GLAND*

SAMUEL L. GARGILL, M.D.,† AND MARK FALCON LESSES, M.D.‡

BOSTON

SINCE 1942, when the last review of this subject appeared in the *Journal*,[1] there have been many important advances in the understanding of the biochemistry and physiology of the thyroid gland. In addition, a new group of substances that are goitrogenic and at the same time markedly depress thyroid function have been extensively investigated. Radio-iodine, which has been widely used in the investigation of thyroid physiology and iodine metabolism, has reached the stage of clinical usefulness in the treatment of toxic goiter. The value of blood iodine studies continues to be demonstrated, with chief emphasis on the protein-bound iodine of the serum. Finally, there has been further study of the cause of exophthalmos in animals, as well as some clarification of the clinical problem involved.

THE THYROID HORMONE

The diverse actions of the thyroid hormone on bodily functions are fairly well known, but the exact chemical nature of the hormone and the mechanism of its biosynthesis have not been completely elucidated. It has been established that the hormone itself lies somewhere between the large moleculed protein, thyroglobulin, and the relatively simple, iodine-containing amino acid, thyroxine, if in fact it is not either. Harington[2] has contributed new evidence that favors the view that the circulating or effective form of the hormone is thyroxine. It has long been accepted that thyroxine produces every symptom of clinical hyperthyroidism except exophthalmos and conversely is capable of relieving every symptom of myxedema, whether clinical or experimental. It has not been possible, however, to demonstrate a direct effect of thyroxine on normal surviving tissues in acute experiments of several hours' duration. Craig and Salter[3] believe that the thyroid hormone is not thyroxine because of the failure of thyroxine, when added to normal blood, to induce the calorigenic action in excised surviving tissues that was readily produced by the blood of thyroxinized animal. The authors themselves remark on the high degree of variability in their data but consider their conclusions statistically valid. In addition, the physiologic activity of the thyroid

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gland has been claimed to parallel its total iodine rather than its thyroxine iodine content.[4] Although Harington dismisses the evidence as scanty, if true, it invalidates the hypothesis that thyroxine is in fact the circulating hormone and has directed attention to the parent protein, thyroglobulin, or a peptide derived therefrom.

Sensitive immunologic precipitin tests,[5] however, have failed to reveal circulating thyroglobulin, which is active orally in the thyroidless animal. If it were the true hormone one would therefore have to assume that after its degradation for absorption by the intestinal tract it was resynthesized in the absence of the thyroid gland. More direct evidence excluding thyroglobulin itself as the circulating hormone has been offered by Bassett, Coons and Salter,[6] who found the major part of the circulating iodine in the albumin fraction, although the highest concentration of iodine was in the alpha and beta globulins.

Harington[2] presents immunologic experiments that strongly support his view that thyroxine is the thyroid hormone. He immunized animals with thyroxine-protein complexes, whose antigenic specificity was determined by thyroxine and di-iodotyrosine groups, to produce an antiserum whose antibodies were specifically adapted to combine with the molecule of the physiologically active substance and consequently to interfere with the action of this substance in another animal by a process analogous with passive immunization. The antiserums thus developed against the artificial thyroxine proteins did not lower the metabolic rate of normal animals, but they did prevent, almost completely, the characteristic rise in metabolic rate caused by the administration of either thyroglobulin or thyroxine. This neutralization of the effect of thyroxine by the antiserums showed that the circulating antibodies, which contained combining sites adapted to thyroxine, interfered with the access of the latter to its normal sites of action in the tissues. This conclusion is supported by earlier work of McClendon and his associates,[7] who found that the calorigenic action of thyroglobulins from goiters of all types depended on their thyroxine content only and concluded that this content rather than total iodine determined calorigenic effect.

If the circulating hormone is thyroxine or some other hydrolytic product of thyroglobulin, the gland itself should contain an enzyme system capable of breaking down thyroglobulin by proteolysis into smaller components that can pass across cell membranes. The existence of such an enzyme system has been demonstrated and its activities quantitated by DeRobertis and Nowinski,[8] who found a 100 per cent increase in proteolytic activity in the thyrotoxic gland as compared to the normal, and a 25 per cent decrease in iodized thyrotoxic glands and in nontoxic diffuse goiters.

Meyer and his co-workers,[9] by injecting thyroglobulin, produced an immune serum that was effective in producing passive immunization against thyroglobulin in normal rabbits as determined by a reduction in the metabolic rate and the prevention of an increase in metabolic rate from injections of the same thyroglobulin used as an antigen.

Thyroxine synthesis had been accomplished in the laboratory by Harington and Barger[10] in 1927. Proof of the steps in the biosynthesis of thyroxine has been furnished by radio-iodine studies. The progression from the iodine-free amino acid tyrosine to the physiologically active tetra-iodo-thyronine or thyroxine by way of di-iodotyrosine, although logical, had not been established biogenetically. The total iodine content of the thyroid gland is accounted for by thyroxine and di-iodotyrosine, both of which have been shown to occur abundantly in the thyroid gland. What accomplishes the coupling of di-iodotyrosine to form thyroxine? Insight into this mechanism was first clearly furnished by Ludwig and von Mutzenbecher,[11] who were able to iodinate casein, producing products whose physiologic activity was shown to be due to the formation of thyroxine. This remarkable synthesis has since lent itself to the inexpensive production of iodinated proteins of considerable physiologic potency that have been found useful in animal husbandry in increasing milk yield.[12,13] Only two mechanisms are available to explain this formation of thyroxine: either the protein contained thyronine (thyroxine less all four of its iodine atoms), which directly added iodine to form thyroxine, or the iodine produced di-iodotyrosine from tyrosine and was then converted into thyroxine. Proof that the latter type of conversion could occur in minimal amounts was first adduced by von Mutzenbecher[14] in 1939 and was shown by Harington and Pitt Rivers[15] to depend on biologic oxidations. The final proof of the ability of thyroid tissue to convert di-iodotyrosine into thyroxine was furnished by tracer studies utilizing radio-iodine. This was accomplished by two methods. In the first, radioactive iodine was injected into animals and the distribution of radioactivity in the body subsequently determined; in the second, the respiration of thyroid-tissue slices was studied in a medium to which radioactive iodine had been added and whose fate could be traced.

Following the injection of radio-iodine into animals, there is rapid concentration of iodine in the thyroid gland.[16–19] This occurs within a matter of minutes and proceeds until as much as 50 per cent of the radioactive material is found in the gland after forty-eight hours. The radioactive iodine is distributed among three fractions — inorganic iodide, di-iodotyrosine and thyroxine — with increasing amounts of di-iodotyrosine and thyroxine with the passage of time. In fact, Morton and his co-

workers[20] have repeatedly shown that with tracer doses almost all the radio-iodine deposited in the thyroid gland is organically bound within an hour.

When large amounts of radioactive iodine are added to the medium in which surviving thyroid-tissue slices are respiring, there is rapid incorporation of the radio-iodine in the tissue. As in the experiments in vivo, the radioactivity is first associated with di-iodotyrosine and later appears with thyroxine, indicating the same process of conversion as in the intact animal.[21, 22] It is of interest, however, that Schachner, Franklin and Chaikoff[23] demonstrated that surviving thyroid slices were able to concentrate up to 60 per cent of added radio-iodine even after the inhibition of thyroxine and di-iodotyrosine formation by azide or sulfanilamide. Cyanide and sulfide, in addition to inhibiting thyroxine and di-iodotyrosine formation, blocked the accumulation of radio-iodine by thyroid slices. From this selective blocking of iodine concentration and thyroxine formation, the authors concluded that thyroid tissue possesses a mechanism for concentrating iodine that does not depend on conversion of inorganic iodide to thyroxine and di-iodotyrosine.

This group of investigators[24] has directed attention to the importance of an enzyme system in the biosynthesis of thyroxine, first by demonstrating that homogenized thyroid tissue has lost its capacity to incorporate radioiodine, thus proving the need for cellular organization, secondly, by showing that the incorporation does not occur with complete anaerobiasis, and thirdly by blocking di-iodotyrosine and thyroxine formation from inorganic iodide in thyroid slices by typical inhibitors of cytochrome oxidase, such as cyanide, azide, sulfide and carbon monoxide. Dempsey[25] has demonstrated the presence of cytochrome oxidase in the cells of the thyroid follicle and has also presented evidence for the presence of peroxidase in the thyroid cells. He found that the peroxidase reaction was easily inhibited by thiouracil, whereas the cytochrome oxidase reaction was unaffected. This has been confirmed by DeRobertis and Grasso[26] regarding peroxidase activity and the inhibitory effect of thiourea.

Harington and Pitt Rivers[15] postulate that the enzymic oxidizing system liberates iodine from iodides and this free iodine is the effective oxidizing agent that both converts tyrosine to di-iodotyrosine and vice versa. Keston[27] lends support to this view by the demonstration that iodine and oxidases participate in the reaction that organically binds iodine. Recently, Reineke and Turner,[28] after a study of the factors influencing the iodination of casein, concluded that manganese is probably also an important catalyst that acts in promoting thyroxine formation in vivo. Ray and Deysach[29] had earlier shown the particular ability of the thyroid to store manganese. The biosynthesis of thyroxine is thus seen to be intracellular, aerobic and enzymatic.

The effect of hypophysectomy on thyroxine synthesis in the organism has also been studied with the use of tracer doses of radio-iodine.[20] The incorporation of iodine into the thyroid gland was much slower and in lesser amounts in hypophysectomized animals. The conversion of iodide to di-iodotyrosine was unimpaired, but the formation of thyroxine was greatly diminished or almost inhibited.

The extrathyroidal production of thyroxine or thyroxinelike substances by iodination of proteins in the test tube has directed attention to the possibility of a similar synthesis in the thyroidless organism. Chapman[30] found that the level of iodine intake had a significant effect on the weight, surface area, metabolic rate and food utilization of thyroidectomized animals, those with higher iodine ingestion showing an effect that suggested to the author that iodine might play a role in the production of a thyroxinelike substance in the tissues. This aspect of extrathyroidal hormone production was firmly established by Chaikoff and his collaborators[31] through the use of radio-iodine as an indicator. From two to eight months following thyroidectomy, radio-iodine was injected into young rats, which were then killed at intervals of two to ninety-six hours after the injection. The liver, muscles and small intestines showed measurable quantities of labeled thyroxine and di-iodotyrosine. The completeness of the thyroidectomy was checked both by serial section and by the radio-autographic technic. These experiments indicate that tissues other than the thyroid maintain a primitive ability to elaborate a thyroidlike substance. This is confirmation of the concept of Means[32] regarding the priority of the hormone over the gland in the evolutionary scale, the evolution of the gland representing a more efficient method of hormone production.

The Antithyroid Goitrogens

Compounds that possess antithyroid properties fall into two general categories: those that act without producing goiter, of which iodine and radioactive iodine are examples; and those that cause marked hyperplasia and at the same time depress thyroid function. The latter embrace the cyanides, thiocyanates, sulfonamides and thiourea, with its derivatives. This subject has been extensively reviewed by Williams[33] and by Riker and Wescoe.[34]

The goitrogenic action of cabbage, demonstrated in 1929 by Chesney, Clawson and Webster,[35] was shown by Marine et al.[36, 37] to be common to the entire genus of Brassica and to be due to contained cyanides. The condition produced was in essence an iodine-deficiency goiter, since it could be prevented by administered iodine and was due to

increased thyroid activity caused by depressed oxygen consumption from the cyanide. Depressed oxygen utilization increased thyroid activity; goiter results if iodine is lacking in the face of added demands on the thyroid gland.

That the thiocyanates in addition to the cyanides exert a goitrogenic and antithyroidal effect was first observed by Barker[38, 39] in hypertensive patients under treatment with potassium thiocyanate. Many similar cases subsequently reported have been reviewed by Estes and Keith.[40] These goiters occur in about 4 per cent of such patients[39] and are characterized by thyroid hyperplasia, the signs and symptoms of myxedema, occasionally by exophthalmos and by an increased urinary excretion of inactivated thyrotropic hormone. Rawson and his co-workers[41, 42] believe that the thiocyanate prevents the synthesis of thyroid hormone at some point distal to the uptake of iodine, since they were able to demonstrate excessive uptake of radioiodine by thiocyanate-induced goiters. Decreased hormone elaboration leads to hypometabolism and to stimulation of the anterior pituitary body, with excessive production of thyrotropic hormone. This causes thyroid hyperplasia without a corresponding increase in hormone output — "a hyperplasia of frustration." The administration of desiccated thyroid prevents or relieves thiocyanate goiter.

Thiocyanate therapy may also cause acute goiter clinically resembling thyroiditis[43] and pathologically showing extreme parenchymatous hypertrophy and hyperplasia[44] but without papillary infolding or lymphocytic infiltration. The colloid stains well, and the irregularity of the acini and a tendency toward invasiveness suggest neoplasia.

The antithyroidal and goitrogenic properties of the cyanides and cyanates were of experimental and toxicologic interest but failed of clinical application. In 1941, however, British and American investigators simultaneously revived interest in the chemotherapeusis of Graves's disease by parallel studies of new antithyroidal goitrogens. Kennedy and his co-workers[45] found that Brassica-seed diets produced large goiters in rats in spite of simultaneously administered iodide; the goiters required the presence of thyrotropic hormone for development or maintenance, since they did not develop in hypophysectomized animals and regressed after hypophysectomy.[46, 47] The active goitrogenic principle was demonstrated to be thiourea or allyl thiourea.[48]

Meanwhile, Richter and Clisby,[49] in searching for an improved rat poison, discovered that phenyl thiourea caused marked hyperplasia of the thyroid gland. Somewhat earlier, the MacKenzies and McCollum[50] found that sulfaguanidine caused marked thyroid hyperplasia.

In this initial phase of study, chief emphasis had been placed on goitrogenesis — an iteration of the early work with the cyanides and cyanates. Astwood and others[51] and simultaneously the MacKenzies[52] directed attention to the more important effect of these compounds as inhibitors of thyroid function. Both groups of investigators first studied the sulfonamides and thiourea, finding the latter many times more effective than the former as an antithyroidal drug. Both caused thyroid hypofunction, with reduced oxygen consumption and impairment in growth and development. The thyroid glands were enlarged, hyperemic and hyperplastic, with decreased colloid and increased acinar-cell height. Papillary infoldings of the epithelium were frequently observed. Omission of the drugs was followed by histologic and physiologic return to normal.

The shifting of emphasis from goitrogenesis to antithyroidal activity was followed by widespread research into the compounds that maximally depressed thyroid function and were only incidentally productive of thyroid enlargement. Thiourea, thiouracil and their derivatives were found to be the most potent compounds for inhibiting thyroid function.[53] In a more recent study of over two hundred and twenty substances, Astwood, Bissell and Hughes[54] found two types of chemical structure associated with antithyroidal activity. The more active substances were derivatives of thiouracil and possessed a thiocarbonamide grouping; the less active substances possessed an aminobenzene group, such as the sulfonamides, and were a fourth as active as thiouracil. The most active of the former group proved to be 6-N-propyl thiouracil.

To this "periodic table" of antithyroidal goitrogens established by Astwood, other investigators[55–61] added and undoubtedly will continue to add various active compounds, since the slightest shift in chemical structure or linkage produces marked pharmacologic differences.

The morphologic and physiologic effects of these compounds, particularly thiouracil, have been abundantly studied so that an accurate postulation of the mechanism of hormone inhibition can be constructed. Thiouracil retards growth, induces cretinism in newborn rats and antagonizes the effects of injection of the growth hormone of the anterior pituitary body.[62, 63] The presence of the pituitary is essential for the production of goiter with these drugs,[48, 51, 52] since no thyroid hyperplasia occurs in hypophysectomized animals following their administration; in fact, the thyroid gland regresses as in untreated hypophysectomized animals. The goitrogenic effect results from pituitary stimulation and not from direct action by these compounds on the thyroid parenchyma.

No increase of thyrotropic hormone is demonstrable in the blood or hypophysis of rats treated with thiourea or sulfadiazine; in fact, there is a decrease as compared with marked increases found in thyroidectomized animals.[64] Animals pretreated with thiourea and then thyroidectomized showed an increase of thyrotropic hormone in the blood

and a decrease in the pituitary gland. These investigators[64] state, "Thiourea and sulfadiazine, by depressing the formation of active thyroid principle, cause an increased release of thyrotrophin from the pituitary into the blood where, however, it appears in reduced amount because of its removal and increased utilization by the enlarging thyroid gland." Although the decreased amount of the thyroid-stimulating hormone found in the pituitary glands of the drug-treated animals is not explained, it has been shown by Albert et al.[65] that physiologically inactive amounts of these goitrogens augment the action of the thyroid-stimulating hormone when mixed with it in vitro. This synergism is also illustrated by the greater hyperplasia of the thyroid gland in animals treated with both thiouracil and thyrotropic hormone as compared with that in animals treated with either alone.

Whereas the goitrogenic action of the cyanides and probably of the cyanates could be inhibited by iodides, this was not found to be true with the thiourea derivatives,[66] which were in fact iodine-resistant goitrogens. But thyroxine or desiccated thyroid was early shown to prevent and abolish the goitrogenic and antithyroidal effect of these compounds as well as of the sulfonamides,[52, 53] indicating that they do not function by inhibiting the action of the thyroid hormone in the blood or peripheral tissues. Moreover, Malkiel[67] has found no destructive or inactivating effect of thiouracil and sulfaguanidine on endogenous circulating thyroxine.

The effect of the antithyroidal goitrogens on the metabolism of iodine has been explored by conventional technics and through the use of radioactive isotopes of iodine. Thiouracil and sulfadiazine have been shown to cause nearly complete disappearance of iodine from the thyroid gland in five days.[68] This effect is inhibited by removal of the hypophysis or administration of thyroxine. Iodine reaccumulates after withdrawal of the drug, but this reaccumulation is retarded by hypophysectomy or the administration of thyroxine. The relation between the dose of thiouracil and thyroid weight and iodine content is quantitative enough to be used for the assay of new compounds.[68, 69]

By studies of thyroid slices with radioactive iodine in vitro, Franklin and Chaikoff[70] found that the sulfonamides inhibited the formation of di-iodotyrosine and thyroxine but did not alter the absorption of inorganic iodide from the surrounding medium. Thiouracil and thiocyanate were similarly shown by these investigators[71] to depress or inhibit the formation of thyroxine and di-iodotyrosine in vitro. They differed in their effect on iodine concentration by thyroid slices, however, thiouracil having little effect and thiocyanate causing marked depression of iodine uptake by the surviving tissues.

The inability of large amounts of iodine to overcome the stasis of hormone production caused by thiourea was demonstrated in rabbits by Baumann, Metzger and Marine,[66] who showed that the drug caused rapid decrease in both thyroxine and nonthyroxine iodine in the gland itself, with excretion of the excess iodine in the urine. Further studies in vivo with radio-iodine have confirmed the result of the studies in vitro — namely, that thiouracil interferes in the living animal with the incorporation of iodine into thyroxine and di-iodotyrosine in the thyroid gland[72] and thus causes cessation of hormone synthesis.

Further details of the mechanism of action of thiouracil on iodine metabolism have been supplied by studies on the chick with radio-iodine. It was first demonstrated that thyrotropic hormone produces thyroid hypertrophy within twenty-four hours,[73] but no increased iodine uptake occurred until hyperplasia was marked. This accelerated uptake was not maintained with continued stimulation. In addition, thyrotropic hormone caused early and striking acceleration in the loss of radio-iodine from the gland, so that 75 per cent of the quantity initially stored was lost during the first day. This is interpreted as being due to "accelerated secretion of thyroid hormone from the gland induced by thyrotropic stimulation."

Next, a comparison was made of the effects of thiouracil and of thyrotropic hormone on the collection of radio-iodine and on the histology of the thyroid gland in the chick.[74, 75] The histologic changes produced were indistinguishable except for a lag of five days in the appearance of alterations caused by thiouracil. Within an hour after the injection of thiouracil, however, maximal inhibition of the uptake of radio-iodine occurred, with a gradual loss of this inhibitory effect over twenty-four hours. Following the withdrawal of thiouracil, the glands of the treated chicks collected radio-iodine in larger quantities than did those of the controls, in amounts similar to those collected by glands made hyperplastic with injections of thyroid-stimulating hormone. The inhibition of iodine collection resulting from thiouracil in the intact thyroid gland contrasts sharply with the in vitro studies previously described,[71, 72] but both sets of experiments confirm the hypothesis that thiouracil interferes with hormone synthesis by interfering with the metabolism of iodine. Thiouracil inhibited collection of radio-iodine by normal chick thyroid and by that made hyperplastic through thyroid-stimulating hormone and with thiouracil. Salter, Cortell and McKay[76] reached similar conclusions concerning the role of thiouracil — that it prevents the conversion of iodide to di-iodotyrosine and thyroxine without, however, impeding the synthesis of uniodinated thyroid protein.

A more recent study by Chaikoff and his associates[77] has confirmed the depressing effect of potassium thiocyanate on the uptake of radio-iodine by thyroid tissue, either in vitro or in living animals

maintained on an iodine-poor diet. Following the disappearance of potassium thiocyanate from the circulation, the whole gland does have an increased uptake of radio-iodine, but this increase is not apparent when expressed in terms of unit weight of tissue. Thus, the drug does interfere with the removal of iodine from the circulation when iodine is not readily available in the diet. It also inhibits conversion of inorganic iodide to di-iodotyrosine and thyroxine, as shown by low thyroxine content of the gland and decreased levels of protein-bound iodine in the blood. VanderLaan and Bissell[78] have likewise confirmed this course of events by showing that rats fed propyl thiouracil readily take up radio-iodine in their thyroid glands but retain it only for a short time, possiby because it is not hormone-bound, and that in the presence of both propyl thiouracil and potassium thiocyanate there is delayed and only moderate iodine uptake by the gland. They conclude that "in the presence of thiocyanate the ability of the thyroid gland depleted of iodine to take up injected iodine is considerably impaired." These recent studies indicate the importance of time relations in the study of the influence of goitrogens on iodine uptake.

The evidence that the biosynthesis of thyroxine is intracellular, aerobic and enzymatic has been discussed above. The iodination of tyrosine to di-iodotyrosine requires liberation of iodine from iodide. The formation of di-iodotyrosine and thyroxine is "linked with aerobic oxidations involving the cytochrome-cytochrome oxidase system."[24] The effect of the sulfonamides and thiouracil on this enzyme system is controversial, Franklin and Chaikoff[79] observing no effect with the sulfonamides and Dempsey[25] noting that thiouracil readily inhibited the peroxidase reaction in thyroid tissue but did not affect the cytochrome oxidase reaction. McShan, Meyer and Johansson[79] found no inhibition of cytochrome oxidase or of succinoxidase in thyroid tissue by sulfonamides and thiouracil. On the other hand, Paschkis and his co-workers[80] report that thiouracil and the sulfonamides inhibit the cytochrome oxidase in vitro as well as in the thyroid gland itself. Bevelander,[81] after studies on sea-urchin egg development, concluded that thiourea acts by inhibition of enzyme systems necessary for the growth of the sea urchin. Tipton and Nixon[82] observed significant depression of succinoxidase and cytochrome oxidase in the liver of rats.

Thiouracil acts by preventing iodination and hormone synthesis, but it is still not clear whether it acts as an antioxidant, through depression of the enzyme systems or by some mechanism other than that of inhibition of oxidation.

Thiouracil and Related Compounds

Clinical Use

Since Astwood[83] first used thiourea and thiouracil in the treatment of hyperthyroidism, numerous reports have appeared dealing with many thousands of cases. The experience with thiouracil is extensive, but its toxicity has led to clinical studies with other derivatives and related compounds. Excellent reviews concerning large series of cases treated with thiouracil for long periods have been published by Astwood,[84] Barr and Shorr[85] and Williams.[86]

The anatomic effects produced in the human thyroid gland by thiouracil have been chiefly studied in the hyperplastic gland of Graves's disease. The size of the gland may increase, decrease or remain unaltered, but the gross increases in human beings have not been so striking or so constant as those in experimental animals. Prolonged treatment has usually resulted in a decrease of the gland[87] unless myxedema supervenes. Histologically, however, there is great similarity to the experimental effect, with increased thyroid hyperplasia, loss of colloid and increased vascularity.[88, 89] Changes in the pituitary gland similar to those found in animals — increased basophilism and absent eosinophilism — have been reported.[90]

Physiologically, thiouracil decreases the basal metabolic rate, frequently at the same rate as iodine,[84, 88] and in many cases causes clinical myxedema if continued for several months.[84, 85] Myxedema, however, has not yet been conclusively produced by thiouracil in persons with normal thyroid function,[84] the normal economy evidently possessing adequate homeostatic mechanisms for resisting the usual goitrogenic and thyroid-depressing effects of this compound. Following the administration of thiouracil in Graves's disease, the uptake of tracer doses of radio-iodine is greatly diminished with an increased urinary excretion,[88] as previously described in animal studies. The hormonal iodine of the blood returns to normal,[91] the blood cholesterol rises,[92] the calcium, phosphorus and protein balances become more positive and creatinuria decreases.[93] In general the physiologic effects produced are such as would occur with amelioration of thyrotoxicosis and a return to the euthyroid state. These changes, which occur far more regularly than with iodine therapy, may take from several weeks to several months for completion.

The effective dosage of thiouracil for initial therapy is generally 0.6 gm. daily, in doses of 0.1 gm. at regularly spaced intervals. The dosage is reduced as the basal metabolic rate approaches normal, and maintenance doses of 0.05 to 0.2 gm. are utilized for long periods. Intermittency of treatment is avoided, since it is considered to be a contributing factor in toxic reactions. Subjective and objective clinical improvement usually appears within seven to ten days after the initiation of therapy. The basal metabolic rate and blood-cholesterol levels serve as adequate laboratory guides in the regulation of dosage.

Thiouracil has been used in two ways: as the sole agent in the control of thyrotoxicosis to produce a

so-called "chemical thyroidectomy" and in the preoperative preparation of patients for thyroidectomy, either alone or in association with iodides.

When thiouracil was used as the sole agent in the treatment of Graves's disease, about 50 per cent of patients remained in remission and the other 50 per cent relapsed within two weeks to five months.[84–86] In general, patients treated for nine to twelve months had a smaller relapse rate than those treated for shorter periods, but Williams[86] obtained remissions lasting as long as twenty months in several patients who were under treatment for only two months. On the other hand, relapses occurred in several patients who had been treated for as long as twenty months. Lasting remissions occurred more frequently in female patients with small glands and mild hyperthyroidism.

The use of thiouracil in the preparation of the patient for thyroidectomy has been extensively reported[94–96] and has established itself as the agent of choice for severe cases of thyrotoxicosis because it almost invariably reduces the metabolism to normal and renders a one-stage thyroidectomy feasible in patients who previously required multiple operations. When thiouracil is used as the sole drug, however, the gland is so vascular and friable that hemostasis is arduous and the gland more difficult to handle. Fortunately, the addition of iodides in the preoperative preparation, either in conjunction with thiouracil or for a period of seven to fourteen days preceding the operation, greatly reduces the vascularity and allows adequate control of bleeding at operation. In our experience the two drugs may be used simultaneously up to operation, since thiouracil and its derivatives do not repress the involuting effect of iodine on the hyperthyroid gland.[85, 88, 97]

During the early experience with thiouracil in the treatment of toxic goiter, it appeared that preliminary administration of iodide slowed the rate of improvement, and it was believed that this was due to the effect of iodine in causing increased hormone storage. More extensive experience has shown that there is considerable variation in the effect of iodide on subsequent thiouracil therapy in Graves's disease,[84, 87] and this has been our experience. In rats simultaneous administration of sodium iodide and methyl thiouracil resulted in the typical iodide effect — flattening of the epithelium and colloid accumulation. The same investigator[98] found greater inhibition of thyroid function when both substances were administered to thyrotoxic patients than with either alone, and concludes that no specific antagonism between the effects of goitrogenic substances and iodine is apparent; iodine and the thyrotropic hormone or the goitrogens must be supposed to have different points of attack, since the two phases can be accelerated co-ordinately. Danowski, Man and Winkler[99] also found that previously administered iodine did not significantly interfere with the subsequent antithyroidal effect of thiourea.

The inter-relation between thiouracil and iodine as they affect the hyperplastic gland in Graves's disease has led to a reformulation of the mode of action of iodine in this disease by the Thyroid Clinic of the Massachusetts General Hospital.[100] The function of iodine in supplying an essential ingredient for thyroid economy is termed its "iodinating action," which may be served by as little as 0.075 mg. of iodine daily. In Graves's disease the rapid manufacture of thyroid hormone creates an iodine uptake by the gland two or three times that in normal persons. The administration of iodine in daily doses of 6.0 mg. or more meets the demands of increased hormone production and thus induces regression of the gland toward normal — the so-called "involuting action" of iodine. Under thiouracil treatment the hyperplastic gland in Graves's disease becomes more hyperplastic. In spite of the fact that thiouracil prevents the utilization of iodine for hormone synthesis, the iodine causes involution of the thyroid gland in Graves's disease. Therefore, it is concluded that iodine exerts an iodinating and an involuting action on the gland in Graves's disease and that these two actions can be separated by means of thiouracil.

Toxic Reactions

Early observations quickly showed the varied toxicity of thiourea and thiouracil. The principal toxic reactions comprised the following: dermatitis, drug fever, swelling of the submaxillary glands, leukopenia and agranulocytosis. Less frequent reactions are the following: edema of the legs, purpura, hematuria, Mikulicz's syndrome, pericarditis, periarteritis nodosa and psychosis. These reactions have been described and reviewed extensively.[101–108] In addition, they have been the subject of co-operative studies covering 1091 patients in one group[109] and 5745 in another.[110] It is clear from these analyses of the toxic manifestations in large groups of cases that approximately 15 per cent of all patients will show some type of adverse reaction to thiouracil. All the principal reactions promptly disappear on omission of the drug except agranulocytosis, which is the most serious complication of thiourea and thiouracil therapy and requires special consideration because of its frequently fatal issue. It occurs in about 2.5 per cent of cases, with a varying fatality rate of 15 to 25 per cent and an overall mortality in large series that is constant at 0.4 to 0.5 per cent. Agranulocytosis tends to occur in the early weeks of treatment, but no general rule can be laid down that will guarantee freedom from serious hematologic reactions. As Lesses and Gargill[106] state:

> Dosage, duration of treatment, constant or intermittent therapy, associated clinical phenomena and premonitory symptoms have not proved safe guides. Serious reactions have occurred at both high and low dosage levels, with short and with long treatment and with both constant and intermittent administration of the drug.

Because no protective treatment is available, frequent observation of the patient receiving thiouracil is essential, and white-cell counts should be done three times a week, with estimation of the neutrophil percentage whenever the total white-cell count is below 5000. The patient should be cautioned to report promptly the development of fever, dermatitis or sore throat. If severe neutropenia or agranulocytosis develops, the drug should be promptly omitted and vigorous therapy with penicillin and transfusions should be started.

The unpredictable occurrence of agranulocytosis with thiouracil therapy must be balanced against the risks of thyroidectomy. Since many of these risks are caused by the inability of iodine to induce an optimal remission, the use of thiouracil offers an opportunity to avoid the mortality associated with surgery in severely toxic cases. Although the risks of thyroidectomy are greatest in patients with severe thyrotoxicosis or with associated cardiovascular disease, a fatal reaction to thiouracil may occur in mild or uncomplicated cases. For this reason, thiouracil is best employed as a preoperative agent along with iodine in patients who are severely toxic. The mildly toxic group is best managed with iodine followed by thiouracil and thyroidectomy if iodine alone fails to induce and maintain a complete remission. Thiouracil also has a proper place in the treatment of patients who refuse operation or who are unable to have surgery because of coincidental serious disease or when adequate surgical facilities are not available. Patients with toxic nodular goiters and a small group with exceptionally large diffuse toxic goiters should be subjected to thyroidectomy after preparation with either iodine alone or with thiouracil and iodine, depending on the degree of toxicity. Thyroidectomy is eventually indicated in this group, either because of pressure effects or because of possible neoplastic disease in the nodular goiters.

Continuous therapy with thiouracil, if essayed, should be restricted to patients who can be closely observed and whose temperament and occupation readily lend themselves to such observation. Another hazard of continuous thiouracil therapy is the possibility that it will stimulate carcinogenesis in the thyroid gland. Thiourea, when administered to rats together with the carcinogen acetaminofluorene, produces rapidly growing tumors, which neither alone evokes.[111] Paschkis and his associates[112] found that thiouracil induces mitosis stimulation in rats kept at low temperatures, as measured by the colchicine technic.

The toxic manifestations of thiouracil have led to clinical trials of many related compounds in an effort to circumvent the undesirable side effects. Thiobarbital,[113–115] methyl thiouracil,[116–119] amino thiazole,[120] 6-N-propyl thiouracil[121, 122] and many others have been utilized.[97, 123] The first three proved at least as toxic as thiouracil. Amino thiazole is still under study. Propyl thiouracil in preliminary clinical studies produced only urticarial dermatitis but was highly toxic to rats,[124] so that no final estimation of its toxic potentialities can be made at present. Sensitization phenomena appear to be frequently linked with the toxic qualities of all these compounds.[101–105]

Other Antithyroidal Agents

The effectiveness of the antithyroidal goitrogens depends on their interference with the production of thyroid hormone. They do not in themselves antagonize or neutralize the effect of circulating thyroxine so that they are antithyroidal by indirection rather than specifically. Recently, certain compounds have been claimed to be particularly antagonistic to thyroxine itself. Carter and his collaborators[125] found a substance in ox and whale liver and in human urine — identified as paraxanthine (1, 7-dimethylxanthine) — that was capable of converting the temperature-heart-rate curve of the summer frogs' heart into the curve of the winter frogs' heart. This substance, which was isolated in crystalline form, appeared to counteract the effects of thyroxine in rats. Barker[126] and Williams,[127] however, were unable to find significant antithyroidal action from this drug as measured by effects either on oxygen consumption or on tadpole metamorphosis. It had no observable result when given to a thyrotoxic patient for a period of eleven days.

Mansfeld[128] extracted from the thyroid gland and human serums crystalline substances called "thermothyrin A and B" that are capable of producing as much as a 50 per cent lowering of oxygen consumption in rats. This work has not yet been confirmed, but the compounds involved may be related to certain structural analogues antagonistic to thyroxine investigated by Woolley.[129] These were newly synthesized ethers of N-acetyl di-iodotyrosine that did counteract the pharmacologic effects of thyroxine on tadpoles but that, in the absence of thyroxine, were chemically close enough to it to have a slight thyroxinelike effect themselves. This development may hold promise for eventual isolation of a natural antithyroidal compound without the toxic complications of the thiourea derivatives.

Radioactive Iodine

In 1938 Hertz, Roberts and Evans[16] introduced radioactive iodine as an aid in the study of thyroid physiology. The hyperthyroid gland was found to absorb as much as 80 per cent of small tracer doses of radio-iodine.[130] Its application to the treatment of Graves's disease by Hertz and Roberts[131] and by Hamilton and Lawrence[132] quickly followed. The latter authors reported 3 cases of hyperthyroidism that were completely remitted after adequate doses of radio-iodine. In the former series ordinary iodides were given in addition to the radio-iodine.

Recent progress reports by Hertz and Roberts[133] and by Chapman and Evans[134] deal with the use of radioactive iodine in a total of 51 cases followed up to five years, the former continuing to advocate supplementary iodide therapy following the ingestion of radio-iodine but the latter finding it unnecessary.

Radioactive iodine is prepared in a cyclotron by nuclear bombardment of metallic tellurium that becomes transmuted into iodine. This must be dissolved, distilled and reduced to sodium iodide. The final product as administered is dissolved in distilled water to contain 14 to 79 mc. of twelve-hour iodine. This is ingested by the patient within one to four hours after conclusion of the bombardment. The dosage given is dependent on the estimated weight of the thyroid gland, about 0.5 to 1 mc. of twelve-hour iodine per gram of thyroid being utilized, in doses ranging from 5 to 25 mc. in one series[133] and an average of 40 to 50 mc. in the other.[134] Large doses may cause radiation sickness. Ordinary iodine therapy should be withheld for several weeks before the administration of radio-iodine, to ensure adequate concentration of the radio-iodine by the thyroid gland. Biopsies indicate that radio-iodine causes fibrosis of the gland similar to that seen with external irradiation. Adequate doses, either single or multiple, have caused sustained remissions in about 80 per cent of the patients treated. Personal observations in a small number of cases indicate that single doses ranging from 8 to 25 mc. were frequently ineffective in producing a remission and required supplemental use of iodides.

More data must be accumulated before final judgment can be made of the place of radio-iodine in the therapy of Graves's disease, particularly regarding the undesirable late effects from the "internal radiation." On a theoretical basis the administration of radioactive iodine seems unlikely to produce deleterious late effects. The beta rays emitted have a maximum range of a few millimeters of tissue, and whatever radio-iodine is not absorbed by the thyroid gland is excreted in the urine.

Blood-Iodine Studies

Determination of the blood-iodine level has become increasingly important in the diagnosis and management of thyroid disease. The concentration of precipitable or protein-bound iodine in the serum is probably an index of the amount of circulating thyroid hormone and hence is also called "hormonal iodine." The methods, which are relatively exact but arduous, require considerable skill in the technics of analytical chemistry, so that they are not suitable for routine clinical laboratories. The information obtained, however, is sufficiently valuable to warrant greater clinical use.

Curtis[135, 136] has recently reviewed a large experience extending over thirteen years utilizing whole-blood-iodine levels rather than those of precipitable serum iodine. In toxic goiter, whether diffuse or nodular, the level of blood iodine was consistently elevated to about twice normal (4 microgm. per 100 cc. as contrasted with 8 microgm. per 100 cc.). In his final conclusion, however, he states: "The determination of the basal metabolic rate is a more reliable test of thyroid activity than the level of the unfractionated whole blood iodine. However, both determinations, considered together, are superior to either alone."

Winkler and his collaborators have contributed important studies on the precipitable serum iodine in hypothyroidism[137] and hyperthyroidism[138] and on the effect of ingested desiccated thyroid in subjects with normal thyroid function.[139] In untreated myxedema the serum iodine was characteristically subnormal or absent; treatment with thyroid caused a linear elevation in the level of serum iodine in accordance with the dosage of thyroid, 0.07 gm. (1 gr.) elevating the serum iodine by 2 microgm. per 100 cc. The basal metabolic rate responded more slowly than the iodine levels to alteration in the thyroid state.

In hyperthyroidism at least 95 per cent of all cases had elevation of the precipitable serum iodine. This elevation frequently declined with administration of iodides — occasionally to normal levels — and was restored to normal or subnormal levels following radical subtotal thyroidectomy. Low values frequently persisted permanently, associated with normal metabolic rates but with slight elevations in the serum cholesterol and some clinical evidence of mild hypothyroidism. The level of the serum iodine, therefore, appeared to be more sensitive than the basal metabolic rate in measuring thyroid hypofunction.

When desiccated thyroid was administered to normal subjects there was far less change in the metabolic rate and serum iodine than in myxedema. The administration of 0.7 to 2.0 gm. (10 to 30 gr.) of dried thyroid, however, caused abnormally high serum iodine, an elevated basal metabolic rate and clinical signs of thyrotoxicosis. Although the normal subject was resistant to thyroid, once enough was given to raise the serum iodine, the correlation between rises in that value and the basal metabolic rate was exactly the same as that in myxedematous patients. Two conclusions were drawn from this study: normal tissues are as sensitive to thyroid as myxedematous and the degradation of normal iodine to inorganic iodine by the normal thyroid gland probably explains the tolerance of euthyroid subjects to large doses of thyroid. This paper contains several instructive graphs showing the parallelism between precipitable serum iodine and basal metabolic rate when thyroid is administered.

Exophthalmos in Thyroid Disease

The problem of exophthalmos associated with toxic goiter has continued to excite the interest of investigators and to harass and mystify the clinician. Two exhaustive reviews, dealing particularly with the clinical problems, have recently appeared by Mulvany[140] and Woods,[141] whereas the experimental aspects have been most instructively studied by Albert.[142] Woods summarized the present status of the subject as follows:

> A critical review of all the various theories and experiments in the etiology of the exophthalmos of primary toxic goiter permits but one conclusion — the problem is still unsolved. . . . The evidence indicates that exophthalmos is probably not related to a thyrotoxicosis and not related at all to a sympathicotonia. The weight of evidence would indicate that both the thyrotoxicosis and the exophthalmos are related in some way to the action of an anterior pituitary hormone . . . or several hormones. . . . Any effect by thyroxin appears . . . to influence favorably the exophthalmos. . . . Deficiency in the gonads or adrenal cortex . . . may play a considerable role in the picture.
>
> If the exophthalmos . . . is in truth initiated by an anterior pituitary hormone, the means by which it accomplished this end is still a mystery. The anatomical evidence all points strongly to the impossibility of the eye being pushed or pulled forward by any muscular action. Edema and hypertrophy of the orbital contents with some inflammatory reaction is present but whether this is . . . primary . . . or secondary . . . is undetermined. . . . Once initiated, however, the orbital hyperplasia may continue or persist despite the control of the metabolic phases of the disease.

There is considerable clinical evidence that any measure that quickly and completely alleviates the thyrotoxicosis may worsen the hyperophthalmia of patients with severe or malignant exophthalmos.[143–146] Although this is not invariable, its occurrence is frequent enough so that in thyrotoxic patients with severe ophthalmopathy the effect of any therapy on the eyes should be given first consideration. Ordinarily this would call for gradual control of the thyrotoxicosis, such as with external irradiation, chemical thyroidectomy with thiouracil or iodide or radioactive iodine therapy.[147] A remission induced with radioactive iodine in 1 case did not increase severe exophthalmos.[134] Thyroid administration is perhaps helpful and should be utilized to the point of tolerance for long periods as soon as the intrinsic thyrotoxicosis is brought under control. The work of Winkler[137–139] suggests the desirability of administering enough thyroid to raise the serum iodine to thyrotoxic levels. The determination of the basal metabolic rate can be used as an indirect guide to the level of hormonal iodine if facilities for the latter estimation are not available.

Experimentally Albert[142] has conclusively demonstrated that the anterior pituitary gland contains an exophthalmogenic factor that produces striking exophthalmos in the fundulus — the common Atlantic minnow. This factor parallels the thyroid-stimulating hormone of the pituitary gland both qualitatively and quantitatively and may be that hormone or one closely related. In the fundulus, the exophthalmos is due to secretion of fluid by the orbital tissues into the retrobulbar space. This fluid presses the eyeball forward and thrusts it out of the orbit by overcoming the pull of the extraocular muscles. Albert's work holds definite promise for the future elucidation of the clinical problem of exophthalmos.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32461

PRESENTATION OF CASE

A thirty-one-year-old housewife entered the hospital because of lower abdominal pain.

At 5:00 a.m., eight days before admission, the patient was awakened by a sharp pain in the left lower quadrant, flank and thigh. It was intermittent and severe enough to make her cry out. She desired to move her bowels, but could not. The pain persisted all day, without anorexia, nausea or vomiting. Two enemas were administered. Since only a small portion of the fluid was evacuated, the patient swallowed three tablespoonfuls of milk of magnesia. On the following day the pain spread over the entire abdomen and was constant. A physician prescribed "white pills," fluids and bed rest because of fever. Six days before admission a soapsuds enema initiated a diarrhea that lasted four days. The stools were loose and yellow. The patient felt more feverish, and the abdomen appeared distended; the pain was persistent, but less severe. On the following day she began to have severe cramps over the entire abdomen. Anorexia was marked. This lasted until two days before admission, when the patient began a soft diet; the diarrhea eased, and the pain was less severe. On the day before admission the physician advised hospitalization because of continued fever. By the time of admission the pain was reduced to a dull ache in the left flank and over the symphysis. During this illness there was some urinary frequency but no dysuria.

The patient had had three children, the last one a year before entry. The menses had been normal. The last period had begun twelve days before admission and had lasted three days. Four years before admission she had had a post-partum phlebitis, for which bilateral ligations were performed. For several years varicose veins had caused some pain on standing, and several had been injected.

On physical examination the patient did not appear ill. She weighed 240 pounds. There was diffuse tenderness throughout the lower abdomen without spasm or rebound tenderness. There was a slight white discharge from the cervical os. Motion of the cervix did not cause pain. There was slight tenderness in both vaults, and a large, firm mass was palpated in the right vault that was

slightly movable and did not seem to be attached to the cervix. The fundus was not palpable. The mass was also felt on rectal examination.

The temperature was 101°F., the pulse 96, and the respirations 22. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a white-cell count of 8600, which rose to 10,800 on the fourth hospital day. The urine and stools were normal. X-ray examination revealed a questionable soft-tissue mass represented by an 11-cm. area of decreased density in the pelvis. The cervical discharge was negative for streptococci and gonococci but abundant beta-hemolytic streptococci were cultured from the urine.

In the hospital the temperature remained between 99 and 100°F. On the fourth day the fundus of the uterus was felt anteriorly to the left of the midline, and an operation was performed.

Differential Diagnosis

Dr. Carroll Miller: We have here the record of a young woman — apparently in good health, without previous disease or surgery — who was seized with a sudden abdominal pain whose nature makes one think that it was dependent on an acute abdominal condition. The disease must have been in the lower abdomen, and we should consider three systems in formulating a differential diagnosis. The urinary tract can be dismissed quickly because of the lack of urinary symptoms. It is true that the patient had urinary frequency, but she had no dysuria in the hospital. Beta-hemolytic streptococci were cultured from the urine. It has been found not infrequently that pathologic conditions in the kidney, the ureter and the bladder may produce a picture simulating an acute abdominal emergency. Pyelitis or ureteral stone will cause pain, spasm, nausea and vomiting, an urge to urinate at frequent intervals and sometimes dysuria. The symptoms that this patient presented, however, do not suggest to me either pyelitis or stone, and the microscopic examination of the urine seemed to rule these out after admission.

The gastrointestinal tract, particularly the small and large bowel, should next be considered. In any acute abdominal condition one first suspects appendicitis. Symptoms of appendicitis are unusual on the left side of the abdomen. There may be a malrotation of the colon, with the cecum and appendix on the left of the midline; some information may be obtained from the x-ray film about the position of the colon, even though a barium enema was not done. The progress of the symptoms suggests a sudden rupture or extension of a long-standing process in the lower abdomen that was not, however, sufficiently virulent to cause peritonitis. In cases of ruptured appendix or a ruptured Meckel's diverticulum, one finds evidence of persistent and usually widespread peritoneal infection and inflammation. We should always think of sigmoidal diverticulitis in cases of sudden left-sided lower abdominal pain, but it is rare to have diverticulitis in a person in the early decades of life — this patient was thirty years old, and the usual symptoms occur after forty. It is quite possible that a rupture of an infected diverticulum caused a peritoneal reaction at first, which became walled off, with the formation of an abscess. Again, I think that we can rule out rupture of a carcinoma of the sigmoid or rectum because this patient apparently had had no previous bowel disturbance. Examination of the stools was negative for blood, I assume, and she did not present a history of carcinoma, either from obstruction or from other interference with bowel habits. A volvulus of the sigmoid is something that we see fairly often. This may produce rather low-grade obstruction, which becomes more marked as time goes on. It may cause marked peritoneal irritation as the circulation in the twisted loop becomes impaired. It is unlikely, however, that this patient would have recovered from the condition so easily and so well as she apparently did. The confusing finding that turned up later in the illness is the mass in the right side of the pelvis, when the original pain was experienced on the left.

So far as the internal female genitalia are concerned, I think that we must consider first and always the possibility of extrauterine pregnancy. We cannot always depend on the menstrual history in cases of pregnancy because we have all seen patients two, three or four months' pregnant who have had some flow at the usual menstrual time. We assume that this last period, twelve days before the pain started, was a normal one. The patient was obviously an obese woman, and examination of the abdomen was undoubtedly difficult. She may have had pelvic inflammatory disease, with hydrosalpinx, or diffuse ovarian pseudomucinous cysts. She may have had a simple ovarian cyst that was not large enough to cause symptoms of pressure or pain prior to the onset of the present illness. This may have become twisted during the night before she was awakened with pain, and with increasing infarction it may have ruptured. I should like to believe that this process was primarily a rupture of a small hollow viscus or cyst, with flooding of the peritoneal cavity and with gradual subsidence of the diffuse peritoneal reaction and residual fluid into an abscessed mass. Let us not call it an abscess but encapsulated fluid. I should be interested to know what the hemoglobin determination was when she was examined in the hospital.

Dr. Tracy B. Mallory: The hemoglobin determination is not recorded.

Dr. Miller: I think that we should all like to know what the hemoglobin was, because if there was blood in the abdomen there should have been a fairly moderate reduction in the hemoglobin.

It is quite possible that an extrauterine pregnancy did rupture. The peritoneal irritation was caused by either blood or cystic fluid and accounted for the nausea, the distention, the fever and the urge to move the bowels at first and the diarrhea later. Of course, the magnesia would have influenced the bowel habits. At any rate, there seems to have been some resolution of the process as time went on, so that the mass finally became definitely palpable and the fundus of the uterus could easily be outlined and was found to be pushed over to the left side. There was no question at that time of the location of the mass.

May we see the x-ray films that show the area of decreased density?

DR. MILFORD D. SCHULZ: This film shows the area of density in the pelvis. We should pay particular attention to that. The observer used the term "decreased" density. If that is true, it might be a cyst containing fatty material.

DR. MILLER: It is not delineated enough to call it a loop of bowel with air in it?

DR. SCHULZ: There is no indication that it is a dilated loop of small bowel.

DR. MILLER: I do not get much help from the x-ray film. I should guess that this patient had a ruptured ovarian cyst, with persistent bleeding and subsequent formation of a residual mass. My second choice is a ruptured tubal or extrauterine pregnancy.

CLINICAL DIAGNOSIS

Ovarian cyst.
Pelvic abscess?

DR. MILLER'S DIAGNOSIS

Ruptured ovarian cyst, with hemoperitoneum and hematoma of adnexa.

ANATOMICAL DIAGNOSIS

Dermoid cyst of left ovary, with twisted pedicle.

PATHOLOGICAL DISCUSSION

DR. MALLORY: When the abdomen was opened a moderate amount of orange-colored fluid was seen free in the peritoneal cavity. As exploration was continued a large mass was found adherent to the posterior surface of the uterus impacted in the posterior cul-de-sac. The surgeon's first impression was that it represented endometrial implantation, but on further exploration he found that it consisted of a discrete cyst of the left ovary with a twisted pedicle. It was possible to free it and to remove it without difficulty. When the cyst was opened it was found to contain cheesy material and hair; in other words, it was a dermoid cyst of the ovary, with a twisted pedicle.

DR. MILLER: Had it ruptured?

DR. MALLORY: No.

CASE 32462

PRESENTATION OF CASE

First admission. A seventy-four-year-old woman, a lecturer, entered the hospital because of substernal pain.

For twenty years the patient had had an insidiously developing productive cough that was worse during the winter and when she caught cold. The amount of thick, white sputum gradually increased to an estimated two cupfuls daily at the time of entry. Four years before admission she raised blood-streaked sputum for three days. For several years she had stopped giving long lectures because they made her hoarse. Seven years before admission the patient became dyspneic and gained weight. X-ray examination showed a large heart. With digitalis the symptoms gradually cleared until five years before admission, when a dull ache developed throughout the chest. It was accompanied by exertional dyspnea, anorexia and a loss of 10 pounds in weight. Thereafter the ache was almost constant and was not affected by deep breathing but was made worse by exercise. During these five years there was little change except for increasing fatigability. The day before admission, after walking half a block, the patient felt as if the chest were being squeezed. She walked a little farther and had to call a taxi. The sensation was described as if "something were expanding in the chest" causing pressure and pain that were mostly substernal but radiated all through the chest. She was dyspneic and weak and had difficulty in talking.

The patient had married at the age of nineteen and had one child, who was in good health.

On examination the patient was in no apparent distress except for a cough productive of sticky white sputum every three or four minutes. There were bilateral cataracts obscuring the fundus, although the patient could read. The left heart border extended 10 cm. from the midsternal line in the sixth interspace. The sounds were good. Inconstant, coarse rhonchi, which disappeared on coughing, were heard throughout the chest. The diaphragm was low, and the excursions were poor.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 150 systolic, 90 diastolic, in the left arm, and 130 systolic, 100 diastolic, in the right arm.

Examination of the blood showed a hemoglobin of 12.6 gm. per 100 cc. and a white-cell count of 9400. The urine gave a ++ reaction for albumin, and the sediment contained 35 white cells per high-power field. An x-ray film showed marked dilatation of the ascending arch and proximal descending portions of the aorta. The true diameter appeared to measure about 6 cm. The aorta was tortuous and contained calcifications. The trachea was compressed and displaced toward the right. The pulsations of the aorta were not wide. The left

ventricle was enlarged, and there were areas of focal collapse in both lower lung fields. An electrocardiogram showed a PR interval of 0.21, with a rate of 100. There was moderate left-axis deviation. A second electrocardiogram six days later was normal. The sedimentation rate at intervals of fifteen minutes was 6, 30, 43 and 46 mm. The blood Hinton reaction was negative.

The temperature rose to 100 to 100.5°F. daily. After seven days the patient's condition was unchanged, and she was discharged.

Final admission (eleven days later). After discharge the symptoms were approximately the same as previously until the night before admission, when the patient suddenly experienced a smothering sensation and had difficulty in breathing. This was followed by much coughing productive of white phlegm.

On physical examination there was moderate respiratory distress, with many coarse crackling rales all over the lung fields. The neck veins were engorged, and the liver was palpable. The coughing was accentuated by motion. The heart rate was 130. The respirations were 30. The blood pressure was 132 systolic, 90 diastolic.

Five minutes later the severe dyspnea had disappeared, and the rales were remarkably reduced. During the next twenty-four hours there were two attacks of dyspnea with venous engorgement and rales. Treatment included a total of 24 mg. of morphine, aminophyllin, oxygen and tourniquets. At the end of twenty-four hours the respirations were 9 per minute; the blood pressure was 90 systolic, 62 diastolic. There were a few basal rales bilaterally. The patient died shortly afterward.

Differential Diagnosis

Dr. Conger Williams: I think that it would be well to rearrange the symptoms in the order of their appearance and try to decide what this woman had at the time of admission. First of all, for twenty years she had had an insidiously developing productive cough that was worse during the afternoon. Whether that was related to the terminal episodes, I cannot say; it may have been chronic bronchitis, even of slight degree, or chronic irritation from pressure on a bronchus, although I think that that is less likely. Seven years before admission the patient became dyspneic and gained weight. X-ray studies showed an enlargement of the heart. We might consider some sort of underlying heart disease at that time, but the etiology is not clear in the absence of a history of hypertension or findings suggesting significant valvular disease. It might be that the heart had been enlarged from some underlying chronic heart disease but that the patient at the same time had dyspnea from another cause. Dyspnea from heart disease that clears up for seven years on digitalis alone is rather unusual. It is also possible that she had mild heart disease to begin with, exaggerated by some other complication such as infection or auricular fibrillation, although it is impossible to say which at this point. For five years before admission she had a dull ache throughout the chest, which apparently was constant and was not related to breathing. Constant chest pain, which is unusual and often implies some pressure phenomenon, is a fairly frequent symptom of expanding aortic aneurysm, but is almost unheard of as a symptom of coronary disease over such a long period. Other possible causes of chest pain, constantly present for five years, are few. It is unlikely that an expanding tumor in the mediastinum produced pain in the chest for so long.

Two other symptoms might be considered together. It is stated that the patient stopped giving long lectures because they made her hoarse; I suppose that she was hoarse at other times also. Four years before admission she raised blood-streaked sputum, and it is possible that these two symptoms were related. She may have had a local lesion in the larynx that produced bloody sputum and hoarseness, but I think that that is unlikely. A local malignant tumor of the vocal cords should not persist that long without further complications. Tuberculosis of the larynx might produce blood spitting and hoarseness but is usually associated with widespread pulmonary tuberculosis. I think it likelier that these two symptoms were caused by something lying outside the larynx, probably something in the mediastinum, which not only produced hoarseness by recurrent laryngeal-nerve paralysis but also bleeding by pressure on the bronchial tree.

Another symptom accompanying the constant pain in the chest was described as exertional dyspnea. Whether that was cardiac in origin or related to extrinsic pressure on the bronchial tree, I cannot say at this point.

The next development of importance occurred the day before hospital admission, when after walking half a block the patient felt as if the chest were being squeezed. She also felt as if something were expanding in the chest, which may indeed have been the case. At the same time she was dyspneic and weak and had difficulty in talking. The pain of coronary insufficiency, whether from angina pectoris or from acute thrombosis, is often described as a squeezing or an expanding pain. It is quite possible that this pain that occurred on the day before admission was on a coronary basis. We are not told how long it lasted. Is it known whether it was a matter of a few minutes or hours?

Dr. Edward Bland: The pain lasted all day, from 9:30 in the morning. In the afternoon, when Dr. Davenport saw the patient, she was still having pain, but it was less severe.

Dr. Williams: I think that a blood-pressure difference of 20 points systolic between the two arms

is significant. Such a difference may result from aortic aneurysm, and it is sometimes seen in dissecting aneurysm of the aorta.

DR. JAMES R. LINGLEY: There is marked dilatation of all the thoracic aortic shadow extending up over the arch and down in the descending portion. The heart shadow appears to be enlarged, and there is density at the left base. In this oblique view there appears to be pressure on the left main bronchus. Another thing that I should like to draw attention to is that the calcification in the arch of the aorta has a peculiar rim — instead of being in the periphery it lies 1.5 cm. within the shadow.

DR. BLAND: Could that be due to the position of the patient?

DR. LINGLEY: I do not believe so.

DR. WILLIAMS: Is the left bronchus elevated?

DR. LINGLEY: It seems to be compressed.

DR. WILLIAMS: The early symptoms described before admission certainly suggest, more than anything else, expanding aneurysm of the aorta. There is really nothing inconsistent with that diagnosis except perhaps the long period of survival following the onset of early symptoms, which is unusual for a syphilitic thoracic aneurysm. If the patient had had thoracic aneurysm on a syphilitic basis it would be reasonable to assume that the chest pain resulted from sudden expansion of such an aneurysm. The earlier symptoms of blood spitting, pain in the chest and so forth are classic.

Dissecting aneurysm, of course, should not be overlooked. Cases have been reported in which the patient survived the initial dissection for many years. I am not quite clear about Dr. Lingley's statement of the inner lining of the shadow with calcium, unless it means that the original coat of the aorta was covered over with blood clot. I suppose that that could happen in a leaking saccular aneurysm of the aorta or dissecting aneurysm as well; in the former, blood might infiltrate the outer adventitia. In considering the possibility of dissecting aneurysm, one might quibble over the time of survival following the symptoms that led to admission. Several days elapsed, but it is not too incompatible with dissecting aneurysm for the patient to survive several days before death finally supervenes. From the evidence, I favor a slowly expanding thoracic aneurysm rather than a sudden dissection. It is also possible to have a dissecting aneurysm complicating syphilitic aortitis. Such cases have been reported, in spite of the fact that syphilitic aortitis is supposed to have an annealing action, theoretically effective in preventing dissection. Against the diagnosis of syphilitic aortitis in this case is the patient's sex. The ratios of male to female vary from 5:1 to 8:1, depending on the series recorded. Of course, that is not of importance as a deciding point, nor is the age against the diagnosis of syphilitic aneurysm. The negative blood Hinton reaction is disturbing but is not final evidence against syphilitic infection. The original process could have burnt out or the test may have been negative because of the so-called "zone phenomenon." If the patient had syphilis it was more probably a burnt-out infection.

During the hospital stay the temperature rose to 100 and 101.5°F. daily. Apparently, the house staff was not impressed with the possibility of coronary insufficiency or myocardial infarction to explain the more recent symptoms, because they allowed the patient to go home after a week in the hospital. Nevertheless, I think that this is a possibility, in spite of the apparently normal electrocardiogram. Sometimes, more than a week elapses between the onset of infarction and appearance of the classic changes in the electrocardiogram — as long as three weeks may elapse before a definite diagnosis is possible. I am unable to explain the fever except possibly as a result of myocardial infarction, which would also be consistent with the rapid sedimentation rate.

At the final admission eleven days later, the patient had a smothering sensation and difficulty in breathing followed by coughing, but nothing is said about the character of the cough. There was a slight drop in blood pressure. At this point something else had happened. She developed acute dyspnea and venous engorgement, and the liver was palpable. The best possibility to explain that is congestive heart failure. On that basis, the only explanation we have found so far is myocardial infarction. Another possibility is that this was not heart failure. With aortic aneurysm, especially one involving the arch, it is possible to have obstruction in the venous system supplying the neck and upper extremities by expansion of the aneurysm. If we consider that the acute pain before entry was produced by expanding aneurysm, which is possible, venous engorgement may also have been caused by the same thing. Slightly against that supposition is the fact that no dilated veins were described over the rest of the chest. As a rule, with such complete obstruction, the whole upper venous system becomes distended. If the liver had been enlarged because of venous obstruction, however, that would mean obstruction of the lower systemic venous circuit as well. Such widespread increase in venous pressure is oftener the result of congestive heart failure than of mechanical obstruction.

One other question I should like to bring up regarding the aneurysm is whether this could all have been caused by arteriosclerosis. Arteriosclerotic aneurysm of significant size is more frequently seen along the course of the abdominal aorta than in the chest, although I believe that such aneurysms have been found in the chest. I do not recall ever seeing one that produced a significant mechanical effect by expansion, but I suppose that that is another possibility that must not be overlooked as

a final cause of death to explain the dyspnea. With paroxysmal attacks one might also consider the possibility of pulmonary embolism, but certainly only as a final complicating episode.

First of all, I should say that this woman undoubtedly had an aortic aneurysm. In spite of her age and the negative serologic findings, it was probably syphilitic. I am almost forced to discard a dissecting aneurysm, in spite of the x-ray picture, because I believe that on the evidence presented it is less likely than syphilitic aneurysm. I think it quite likely that the terminal event was the result of myocardial infarction and congestive heart failure.

DR. TRACY B. MALLORY: Does anyone wish to support the possibility of dissecting aneurysm?

DR. BLAND: I should like to add that this patient presented a problem from the psychologic point of view. Quite properly, the question was raised why she went home so soon. Her physicians did not have much choice in the matter.

CLINICAL DIAGNOSES

Aortic aneurysm, arteriosclerotic type.
Coronary occlusion.

DR. WILLIAMS'S DIAGNOSES

Syphilitic aortitis, with saccular aneurysm of thoracic aorta and ? rupture.
Myocardial infarction and congestive heart failure?

ANATOMICAL DIAGNOSES

Syphilitic aortitis, with multiple fusiform and saccular aneurysms of thoracic aorta.
Rupture of aorta, with pseudodissection.
Media necrosis cystica of aorta.
Compression, left main bronchus.
Bronchiectasis, left lower lobe.
Atelectasis, left lower lobe.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The significant pathologic lesion was in the aorta. There was a large fusiform aneurysm involving the entire thoracic aorta and, in addition, localized saccular outpocketings, one of which was just beyond the innominate vein and definitely pressed on and narrowed the bronchus to the left lower lobe. The bronchial tree in this lobe was diffusely dilated. The bronchi were plugged with partially inspissated mucous secretions, and the lobe itself was diffusely atelectatic. The gross appearance of the aorta was characteristic of syphilis, although the process did not extend quite down to the aortic annulus. There were also two rents in the intima of the thoracic aorta, not associated with either of the saccular aneurysms. One of these was quite small and contained a small partially organized blood clot. Beneath the larger rent there was an area of apparent dissection 5 or 6 cm. long filled with partially organized blood clot, some 2 cm. in thickness. On microscopic and gross examination it seemed apparent that this was not a true dissecting aneurysm, which always occurs within the media of the aorta, but a pseudodissection between the outer border of the media and the adventitia — a type of lesion that could occur with rupture of either a syphilitic or a sclerotic aneurysm. The microscopic sections were quite interesting. There were areas presenting all the accepted criteria of syphilitic aortitis, focal destruction of the elastica and muscularis and marked infiltration with lymphocytes and plasma cells in the areas of scarring and also in the form of cuffs around the vasa vasorum. In another part of the aorta there was also characteristic media necrosis cystica, which is the cause of the great majority of dissecting aneurysms. According to standard teaching, syphilitic aortitis and media necrosis cystica are not supposed to exist together in the same aorta. I think that there is no question that in this case they did. It is even conceivable that this was true dissection, although our decision was that it was not. After careful study we found nothing that clearly explained the acute terminal episode. There may have been a little more hemorrhage in the aortic wall, which we could not clearly separate from the previous bleeding. It is quite clear that the majority of the leakage must have occurred at the first attack rather than at the second.

DR. WILLIAMS: What about the heart?

DR. MALLORY: It was normal. There was not much evidence of chronic passive congestion. The lungs weighed 1100 gm. and were moderately edematous. The liver, spleen and kidneys did not show passive congestion.

The New England
Journal of Medicine
Formerly
The Boston Medical and Surgical Journal
Established 1828

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MATERIAL should be received not later than noon on Thursday, two weeks before date of publication.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

GREATER BOSTON COMMUNITY FUND

THE drive to raise the $7,000,000 necessary to support the 1947 needs of the three hundred and thirty Red Feather hospitals and health, youth and social agencies is now in full swing. The question that lies squarely before the people of Greater Boston, according to Mr. John E. Lawrence, chairman of the campaign, is as follows: "Are we going to enable the Red Feather Services of the Greater Boston Community Fund to carry on those humane activities that have made this community renowned for its social consciousness?" The alternative, as Mr. Lawrence points out, is a sharp curtailment of essential services or their maintenance on a bare minimum-need basis — either of which is unthinkable.

The total that must be raised is nearly as large as those of the war years, in spite of the fact that support of certain agencies engendered by the war has been withdrawn. This, however, is not surprising when it is realized that the costs of food, wages and deferred maintenance have increased by at least 40 per cent. "The challenge is put to every one of us," declares Mr. Lawrence. "I firmly believe that the decision will be to keep the community strong. It is up to all of us to force that decision, and I call on every worker and every giver to do just that. We must RING THE BELL!"

A REGRETTABLE INCIDENT

IT IS unfortunate that "Bill" Cunningham, justly celebrated columnist of the *Boston Herald*, should have abandoned all restraint in his column of October 27 that commented on the recent postseason outbreak of poliomyelitis in Newton. At the time of the appearance of this article, 12 cases of infantile paralysis had appeared in that city since October 1, of which 9 had occurred in a certain school district. The school in question had not been closed on account of the outbreak, and this apparently seemed to Mr. Cunningham to have been a dereliction in duty on the part of city and state health authorities and aroused his sense of personal responsibility to the public. Possibly he was somewhat "hypersensitive" to the matter because of certain broad comments he had only recently made concerning pollution of the Merrimac River with poliomyelitis virus, a statement in support of which evidence is still lacking.

Regrettably, Mr. Cunningham in his investigation appears not to have used the probe but rather the bludgeon, and to have become inflamed at, rather than appreciative of, the methods of the highly trained officials who constitute the health departments of both the Commonwealth of Massachusetts and the City of Newton. It is with little real insight into the problems and the difficulties of public-health administration that Mr. Cunningham allowed such a statement as "Health Guardians Need Lesson in Humility to Public, Parents" to appear over his signature; it is unworthy of this protagonist of the common good to attempt to discredit

one of the most valuable agencies that the people of Massachusetts possess.

It is common knowledge that modern, universally accepted public-health methods include keeping schools open during epidemics, except under certain specific circumstances; enlightened health and school officials believe that the safety of children is better guarded by having them under daily surveillance rather than running at large. Furthermore, common sense leads to the conclusion that the public is better served by having its confidence in its deserving public-health servants strengthened, rather than disturbed, by indiscriminate alarms and uninformed criticism. Massachusetts is fortunate in possessing a department of public health with an able, honest and experienced personnel, and Newton has an outstandingly capable health officer. Any attempt at discrediting either of them must be considered as subversive of the public welfare.

The physicians of the Commonwealth should accept the responsibility of maintaining public confidence in these agencies and will no doubt be aided in the task by so honest a journalist as Mr. Cunningham when he realizes the harm that his temporary aberration may have caused.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DWYER — William J. Dwyer, M.D., of Boston, died September 30. He was in his sixty-fourth year.

Dr. Dwyer received his degree from Tufts College Medical School in 1905. He was a fellow of the American Medical Association.

His widow, a son and a daughter survive.

HOLBROOK — Bradbury Holbrook, M.D., of Waltham, died August 24. He was in his seventy-fifth year.

Dr. Holbrook received his degree from University of Pennsylvania School of Medicine in 1899. He was a fellow of the American Medical Association.

HOLT — William L. Holt, M.D., of Amherst, died October 18. He was in his sixty-eighth year.

Dr. Holt received his degree from Harvard Medical School in 1905.

His widow, two sons and two daughters survive.

PULSIFER — Walter H. Pulsifer, M.D., of Whitman, died September 26. He was in his sixty-third year.

Dr. Pulsifer received his degree from Tufts College Medical School in 1908. He was president of the Plymouth District Medical Society and a fellow of the American Medical Association.

His widow and three sons survive.

TERRY — Theodore L. Terry, M.D., of Stow, died September 28. He was in his forty-eighth year.

Dr. Terry received his degree from University of Texas School of Medicine in 1922. He was assistant professor of ophthalmology at Harvard Medical School and was a member of the American Academy of Ophthalmology and Otolaryngology, American Ophthalmological Society, Association for Research in Ophthalmology and New England Ophthalmological Society, and a fellow of the American Medical Association.

His widow survives.

MISCELLANY

HARVARD SCHOOL OF PUBLIC HEALTH

Expansion of Harvard University's School of Public Health through two important faculty appointments and the institution of two new degrees in research were recently announced by Brigadier General James S. Simmons, dean of the school. Those joining the staff are Dr. Hugh R. Leavell, formerly assistant director of the Division of Medical Sciences, Rockefeller Foundation, and Dr. John C. Snyder, former member of the United States Typhus Commission. In addition to degrees that presuppose the qualification of Doctor of Medicine, the school has added the degrees of Master of Science in Hygiene and Doctor of Science in Hygiene, which are open to research workers. Thus the investigation of problems connected with public health, as well as instruction, will be augmented. Dr. Leavell will occupy the chair of public-health practice, which became vacant in July owing to the death of Dr. Edward G. Huber. Dr. Snyder has been appointed professor of public-health bacteriology, a new chair created by the reorganization of the school.

When the United States Typhus Commission was organized during the Second World War, Dr. Snyder was appointed as a member. As such he studied typhus fever at close range in the Middle East and Italy. Since his release from the Army in 1945 he has been in charge of a program of typhus investigation sponsored by the International Health Division.

YALE INSTITUTE OF OCCUPATIONAL MEDICINE AND HYGIENE

Dr. Francis G. Blake, dean of the Yale University School of Medicine, recently announced the establishment of the Institute of Occupational Medicine and Hygiene for work in the field of industrial medicine. The institute, Dr. Blake revealed, will be headed by Dr. Ronald F. Buchan, newly appointed assistant professor of industrial medicine. The primary aims of the institute, according to Dr. Blake, are four in number: the training of medical students and industrial physicians, based on the belief that occupational medicine and hygiene now comprise a specialty; special graduate instruction, together with the opportunity for research in the field of occupational medicine and hygiene, which will be available to graduate students in medicine, nursing, public health and engineering; research in occupational medicine and hygiene, in the belief that the maintenance of active research in such an important field is of teaching value to the intelligent student; and consultation, whereby the institute will assist industrial concerns on certain practical questions in the same fashion as the clinicians in the School of Medicine assist their colleagues with regard to medical, surgical or public-health problems. The establishment of the Institute was preceded by nearly six years of planning and investigation, conducted on the premise that Connecticut, although relatively small in area, is one of the great industrial states and therefore has real need for work in the field of industrial medicine.

The program will be supervised by a special committee composed of the following members of the Yale Faculty: Dean Blake, serving *ex officio*; Dr. William T. Salter, professor of pharmacology; Dr. George M. Smith, research associate in anatomy; Dr. Ira V. Hiscock, professor of public health; and Dr. John R. Paul, professor of preventive medicine. This committee will serve as the co-ordinating group that will work with Dr. Buchan, the clinical director, in plan-

ning the work of the institute at the inauguration of the program. Dr. Buchan, who will sit with the committee, has been practicing industrial medicine in Hartford, where he has been concerned primarily with the organization of medical services for a group of small industrial plants.

BOOK REVIEWS

What People Are: A study of normal young men. By Clark W. Heath, M.D. In collaboration with Lucien Brouha, Ph.D., Lewise W. Gregory, Carl C. Seltzer, Ph.D., Frederic L. Wells, Ph.D., and William L. Woods, Ph.D. A publication of the Department of Hygiene, Harvard University, under a grant from the Grant Foundation. 8°, cloth, 141 pp., with 7 tables. Cambridge: Harvard University Press, 1945. $2.00.

This book is the result of the study of students at Harvard University, begun in 1938. The author, in collaboration with his colleagues, made a study of over two hundred and fifty young men from various points of view. It was not easy to pick out the "normal," for in the first hundred supposedly healthy men studied, seventy-two requested some sort of advice and another twenty-two presented urgent problems, mostly on the basis of a choice of a career, social adjustments or personality difficulties. An attempt was made to study the normal personality and the degree of adjustment to college life — as illustrated by athletic participation and their problems concerning religion, sex and other matters. Physiologic and mental measurements were made, and general medical problems were also investigated. This report discusses various aspects of these problems and is a valuable addition to knowledge in this field. It is only a preliminary study and should lead to more extensive research. The material presented, however, is of interest to physicians, particularly those associated with colleges, and to sociologists, educators and psychiatrists.

Lights Out. By Baynard Kendrick. 8°, cloth, 240 pp. New York: William Morrow and Company, 1945. $2.50.

This is the story of a soldier in World War II from the time he was rendered totally blind by a sniper's bullet, until he was completely conditioned to take his place in the world of today. The psychology of the blind veteran is vividly portrayed, and interesting and accurate descriptions are given of the therapy and methods of rehabilitation practiced at the Valley Forge General Hospital, Pennsylvania, and the Old Farms Convalescent Hospital, Avon, Connecticut. This novel is an important contribution to the medical history of World War II.

Government in Public Health. By Harry S. Mustard, M.D., LL.D. 8°, cloth, 219 pp., with 11 tables. New York: The Commonwealth Fund, 1945. $1.50.

This monograph was prepared at the request of the Committee on Medicine and the Changing Order of the New York Academy of Medicine. The letter of invitation read: "What is wanted is not merely a survey of the present situation, but knowledge of how it came to be, perspectives to help chart the direction of future developments."

The scope of public health is outlined, federal health services, state health departments and local health departments are described, and future trends are discussed. The following quotations from the book describe its contents:

> First, there has always been, and there is now more than ever, a trend toward a more powerful federal government and, second, there has recently developed a strong trend toward a more socialistic federal government. . . . Pertinent in this connection is the fact that public health activities are more and more being considered as an integral part of the developing social security program and are receiving increasing federal attention.
>
> . . . this document is to recognize political and social evolution as it relates to the public health, to view these things as nearly objectively as possible, to regret the passing of earlier concepts and manners, and to confess to a belief that a better public health will result from the changing order.
>
> To those who do not approve of some of the social and governmental trends of today, it is suggested that it is more profitable to recognize their enemy's approach and dimensions than it is just to swear at him after being blinded by temper.

This volume should be read by members of the public-health profession and will be a valuable addition to the library of practitioners of medicine.

NOTICES

ANNOUNCEMENTS

Dr. G. Burnham Beaman announces the removal of his office from Boston to 322 Main Street, Stamford, Connecticut, and the inauguration of a psychiatric service and outpatient clinic in psychiatry at the Stamford Hospital.

Dr. Paul J. Catinella announces the opening of his office for the practice of dermatology and syphilology at 520 Commonwealth Avenue, Boston.

Dr. Samuel H. Marder, having returned from military service, announces the opening of his office for the practice of psychiatry at 419 Commonwealth Avenue, Boston.

Dr. Bernard Yood, recently discharged from military service, announces the opening of his office at 481 Beacon Street, Boston, for the practice of psychiatry and neurology.

EDWARD K. DUNHAM LECTURES

The Faculty of Medicine of Harvard University has announced that the following lectures on the general topic "Biochemical Lesions and British Anti-Lewisite" will be delivered by Dr. Rudolph A. Peters, Whitley Professor of Biochemistry, Oxford University, under the Edward K. Dunham Lectureship for the Promotion of the Medical Sciences:

Monday, November 18. The Significance of Biochemical Lesions.
Wednesday, November 20. The Arsenical Lesion and its Antidote.
Friday, November 22. Clinical Applications and Developments of BAL.

These lectures are scheduled for 5 p.m. at the Harvard Medical School, Building C Amphitheater.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine will be held at the Veterans Hospital, West Roxbury, on Wednesday, November 20, at 8:30 p.m.

PROGRAM

Clinic on Physical Medicine with Case Presentations. Dr. Jacob Rudd.
Medical Rehabilitation in the Veterans Administration. Dr. Sidney G. Licht.
Discussion. Dr. Arthur L. Watkins.

CANCER TRAINEESHIPS

Dr. Thomas Parran, surgeon general of the United States Public Health Service, Federal Security Agency, has recently announced that the National Cancer Institute, which operates as a division of the National Institute of Health, has funds to train approximately thirty physicians in the diagnosis and treatment of cancer. Under a federally financed program, doctors wishing to specialize in this field may be appointed as trainees and be assigned to authorized nonfederal, nonprofit institutions in various parts of the country. Applications for traineeships should be sent to the Director, National Institute of Health, Bethesda, Maryland.

(*Notices continued on page xxi*)